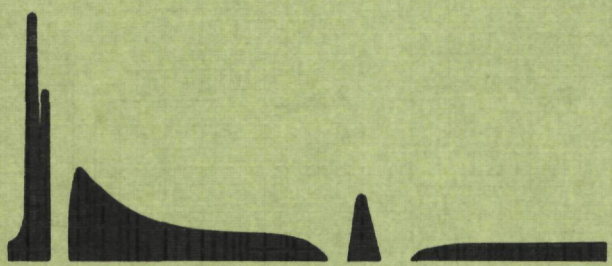
relation between input and output of single units of cat optic tract and lateral geniculate nucleus



a.m.l. coenen

RELATION BETWEEN INPUT AND OUTPUT OF SINGLE UNITS OF CAT OPTIC TRACT AND LATERAL GENICULATE NUCLEUS

PROMOTOR: PROF.DR. A.J.H. VENDRIK

RELATION BETWEEN INPUT AND OUTPUT OF SINGLE UNITS OF CAT OPTIC TRACT AND LATERAL GENICULATE NUCLEUS

PROEFSCHRIFT

TER VERKRIJGING VAN DE GRAAD VAN DOCTOR IN DE WISKUNDE EN NATUURWETENSCHAPPEN AAN DE KATHOLIEKE UNIVERSITEIT TE NIJMEGEN, OP GEZAG VAN DE RECTOR MAGNIFICUS DR. G. BRENNINKMEIJER, HOOGLERAAR IN DE FACULTEIT DER SOCIALE WETENSCHAPPEN, VOLGENS BESLUIT VAN DE SENAAT IN HET OPENBAAR TE VERDEDIGEN OP MAANDAG 13 DECEMBER 1971 DES NAMIDDAGS TE VIER UUR

door

ANTONIUS MATHEUS LOUIS COENEN

geboren te baarlo

NIJMEGEN 1971

Het onderzoek, dat in dit proefschrift beschreven is, is uitgevoerd op de afdeling Medische Fysica (werkgroep Visueel Systeem) van de Universiteit van Nijmegen.

Zonder de hulp van velen zou dit onderzoek niet mogelijk zijn geweest. De Instrumentmakerij (Hoofd de heer K. Peters) ontwikkelde vele mechanische onderdelen, terwijl de Electronica groep van de afdeling o.l.v. de heer J. Bakker meewerkte in de opbouw van de electronische opstelling. De heren Arts en Philipsen van het Centraal Dieren Laboratorium verzorgden de initiële preparatie van de proefdieren.

De belangrijkste bijdrage aan dit werk werd geleverd door de heer C. van Kemenade die assisteerde bij de experimenten en die de gecompliceerde onderzoekingen verlichtte door het ontwikkelen van ingenieuze hulpapparatuur. Tevens was de bijdrage van ir. J. Grupping van het grootste belang voor het verwerken van de experimentele gegevens. Hij ontwikkelde de aanpassing van de opstelling aan de rekenmachine en schreef de computerprogramma's.

In de loop der jaren hebben vier studenten, de heren J. van Gisbergen, C. van Keulen, F. Maes en J. Moors, aan dit onderzoek meegewerkt. Hun deelname heeft het onderzoek op een hoger niveau gebracht.

Dr. H. Gerrits begeleidde het onderzoek met waardevolle suggesties en kritieken. Het onderzoek van de visuele maskering werd samen met Dr. E. Eijkman uitgevoerd.

Dit proefschrift werd getypt door mej. B. Kerbusch, de heer C. Nicolasen tekende de illustraties terwijl de afdeling Fotografie (Hoofd de heer Reijnen) zorg droeg voor de afbeeldingen.

Aan al dezen en aan alle anderen die meewerkten aan het tot stand komen van dit proefschrift mijn dank.

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C O N T E N T S

GENERAL INTRODUCTION

In this study properties of electrophysiologically obtained responses of units in two nuclei of the visual system have been investigated. First, therefore, a brief review of the visual system will be given.

When an image of an object is projected by the eye onto the retina this gives rise to a chain of events in the retina beginning with the absorption of the light by the photo-receptors and ultimately leading to a train of actionpotentials (spikes) generated by the ganglion cells. There are two main classes of ganglion cells. The ON-cells which respond by increasing the spike frequency when the light is switched on and the OFF-cells which increase their activity when the light is switched off. Upon closer examination it appears that the characteristics of these cells are more complicated. Each cell has a receptive field which is defined as the part of the retina which, when stimulated, can elicit a response from the cell. The receptive field consists of a circular center, which gives the ON- or OFF-response as mentioned above, and a surround, lying around the center, which elicits exactly the opposite response. So an ON-center cell has an OFF-surround and vice versa. With these two types of cells, the ON-center OFF-surround and the OFF-center ON-surround cells, the retina is able to encode the visual information of the object.

The axons of the ganglion cells, together forming the optic nerve, transmit the spike activity to the brain. The optic nerves of both eyes partially cross in the optic chiasma. Hereafter the optic nerve, now called the optic tract, runs to the lateral geniculate nucleus in which an up to now relatively unknown processing of the information takes place. This is suggested by the existence of inhibitory interneurons and the endings of non-retinal fibres which indicates influence from other brain structures, for example the reticular formation. There is also electrophysiological evidence for this last point.

In turn the axons of the geniculate neurons, forming the

optic radiation, bring this processed information to the visual cortex. The behaviour of the units of the visual cortex strongly suggests that an analysis of the information takes place here. In particular the complex shape of the receptive fields indicates that, amoung other properties, the shape of the visual objects will be analyzed.

The ON-center OFF-surround and OFF-center ON-surround units are also found on geniculate and cortical levels. The currently well established assumption is that the ON-center units are mediating the perception of brightness and the OFF-center units the perception of darkness.

As mentioned above the role of the lateral geniculate nucleus (LGN) in the visual system is not very clear, in spite of many investigations. The main purpose of this study was to obtain more insight into information processing in the LGN.

A well-known technique for obtaining information about a nucleus in the brain is to extracellularly record the spike response of single units after adequate stimulation. However, when the spike responses to visual stimuli of single LGN units are measured it is clear that these responses are determined by the properties of both the retinal and geniculate units. There are two ways of separately measure information processing in the geniculate units.

Firstly, by means of intracellular or quasi-intracellular recordings from the units. In these recordings the postsynaptic potentials (EPSPs and IPSPs) are also visible which makes it possible to determine the exact input of particular neurons. In Chapter 1 the properties of the quasi-intracellular recordings are analyzed. These measurements, however, have the disadvantage that, due to technical difficulties, the number of investigated units is relatively small.

Secondly, the input to the geniculate neurons can also be measured in the optic tract which is, as mentioned, the pathway from the retina to the LGN. The information processing of the geniculate neurons is then obtained by comparing these responses (input) with the geniculate responses (output). The advantage of the measurements is that many results may be obtained. However, the results are less certain than those from the quasi-intracellular recordings because the responses of the two levels must be compared statistically. This comparison is described in Chapter 2. Moreover in this chapter some additional questions raised during analysis of the responses of the optic tract and geniculate units are also discussed.

All experiments were carried out using cats as experimental animals. Cats were chosen because much morphological and electrophysiological data about its visual system is available. Moreover another important reason was that the visual system of cat is, in many respects, similar to the human visual system. Consequently the investigation of the cat's visual system provides indirect information about the visual system in man.

An important field of investigation is the correlation of electrophysiological findings obtained from animals with perception in man. A good example of the relation between these two types of data is given in Chapter 3. In this chapter data about the visual masking occurring in man are compared with the responses of the peripheral visual system of cats obtained under similar stimulus conditions. This was done in order to find out whether these masking effects were of retinal or central origin.

Chapters 1, 2 and 3 are, as separate papers, submitted to 'Experimental Brain Research'. At this time the first one is in press.

CHAPTER 1

DETERMINATION OF THE TRANSFER RATIO OF CAT'S GENICULATE NEURONS THROUGH QUASI-INTRACELLULAR RECORDINGS AND THE RELATION WITH THE LEVEL OF CONSCIOUSNESS

Introduction

A few years ago McIlwain and Creutzfeldt (1967) made a special type of single unit recording in the lateral geniculate nucleus (LGN) of the cat. They called this the 'quasi-intracellular' recording, because postsynaptic potentials could be recorded while the electrode tip was not clearly inside the cell. However, the exact nature of these recordings is still rather unclear (McIlwain and Creutzfeldt, 1967; Singer and Creutzfeldt, 1970).

The aim of this study was, by means of this type of recording, to obtain more information about the functional role of the LGN in the transfer of the visual information from the optic tract to the visual cortex.

With extracellular recordings Maffei and Rizzolatti (1965) and Sakakura (1968) found that the responsiveness of LGN neurons increased with the level of consciousness of the animal. This level also determines the frequency of the spontaneous activity of LGN neurons. The spontaneous activity increases from sleep to wakefulness and further from wakefulness to rapid eye movement (REM) sleep (Sakakura, 1968; Thomas et al., 1968). Some experimental data suggest that the mechanism underlying these phenomena could be presynaptic inhibition which is controlled by the reticular formation or the visual cortex (Iwama et al., 1966; Angel et al., 1965; Kahn et al., 1967; Suzuki and Kato, 1965; Pecci-Saavedra and Wilson, 1965).

In this study general characteristics of the LGN units were investigated with quasi-intracellular recordings. The input of the LGN units could be determined from the excitatory postsynaptic potentials (EPSPs). As the output is given by the action potentials, the input-output relation of these units is known. This paper is especially concerned with the ratio of the frequencies of incoming and outgoing excitatory events, the transfer ratio. This transfer ratio was determined during different levels of consciousness. This could be done because the experiments were performed on non-anaesthetized paralyzed cats, which showed long periods of sleep and drowsiness alternating with short periods of wakefulness.

The results clearly prove that the flow of visual information through the LGN is modified according to the state of consciousness of the animal. Also by means of these quasi-intracellular recordings, insight could be gained about the mechanism causing the change of the transfer ratio.

A brief report of this work has been presented previously (Coenen and Vendrik, 1971). In a following paper more data about the responses of geniculate and tract units will be given.

Methods

Biological preparation

The experiments were performed on 23 adult cats of both sexes, weighing 1.8 - 3 kg. After premedication with 0.5 mg atropine cats were anaesthetized with a mixture of nitrous oxide and halothane. A tracheatube was inserted orally and a cannula placed in the vena cephalica of the left forelimb. After fixating the animal in a stereotaxic apparatus, paralysis was induced with 60 mg flaxedil administered intravenously and at the same time artificial respiration was started, adding initially anaesthetics to the ventilation gas. Depending on the weight of the animal 30 - 35 cc per stroke was given in a frequency of 25 strokes per minute. This is a light hyperventilation, the carbon dioxide concentration in the expired air being about 5 vol. percents. A rectal thermistor controlled the temperature of the cat. This temperature was automatically held at about 38.5 ^{o}C by means of a heating pad. A hole of 5 x 5 mm in the skull above the right LGN was drilled, and the dura removed. The wound on the head was locally anaesthetized by infiltration of 5 ml 0.5% marcaine, a long acting local anaesthetic. Pressure points of the ear bars were,

before fixation of the head, treated with xylocaine jelly. Pupils were dilated with two drops of atropine and phenylephrine. Eyes were kept moistly with saline during the experiment.

After this initial preparation, which lasted for about one hour, the general anaesthesia was stopped. Half an hour later the experiment started and continued for approximately ten hours. During the experiment paralyzation was maintained by continuously infusing intravenously 5 cc saline per hour containing 10 mg flaxedil and 1 mg d-tubocurarine. After the experiment the animal was killed by an overdose of nembutal. In some cases the brain was removed for a histological examination of the microelectrode tracts.

Microelectrode recordings

Recordings were obtained with glass micropipettes filled with 3 m KCl. The DC-resistance of these electrodes was 2 - 15 megohms which corresponded with tip diameters of about 0.5 - 2 μ. Microelectrodes were stereotaxically placed in the LGN through the overlying brain tissue. The electrode was connected via a chlorided silver wire to a Grass P-16 amplifier with adjustable lowpass and highpass filters and capacity compensation. The frequency bandwidth generally used was 0 - 5000 cps.

Recordings in the LGN could be easily identified as axon or soma recordings. This identification was mainly based on the spike form (Bishop et al., 1962). In the LGN only soma recordings are taken into account. Some control experiments on optic tract fibres were done in the optic tract just behind the optic chiasm.

EEG recordings

The cortical EEG was used as a monitor for the state of consciousness of the cat. This EEG was recorded by means of screw electrodes placed above the frontal cortex. General EEG criteria to interpret the animal's state were used, but the interpretation based on the EEG alone allows only a course classification of the state of consciousness. Mainly three conditions were recognized, the synchronized EEG indicating slow wave sleep, the desynchronized EEG indicating an alert state as arousal or wakefulness and an intermediate state, showing characteristics of both sleep and wakefulness. We interpret this state as a non-alert or drowsy state.

It appeared that the EEG of most cats in our experimental situation showed rather long periods of sleep or drowsiness

alternating with short periods of arousal. Sometimes this arousal appeared spontaneously but mostly it was induced by pinching the cat's tail and lasted usually for a few seconds. This EEG behaviour indicates a good condition of the animal and suggests that the experimental situation causes little discomfort to the cat (Aitkin and Dunlop, 1968; Poggio et al., 1969).

Visual stimulation

The cats faced a translucent screen of 40 x 40 cm, at a distance of 57 cm of the eyes. With a conventional projection system certain objects as spots and annuli could be projected on the back of the screen. These objects could be moved by means of two motor driven mirrors. The light source of the projection system is a Ferranti C1-63 flash tube with rise and decay times of some microseconds. The light of this tube is green with a maximum at 520 nm.

Most experiments were carried out in the light adapted state of the cat, the background intensity being 1 asb (mesopic level). This was the dimmed white light of the room illumination. If this light is switched off the background intensity was 0.01 asb, due to stray light of the experimental set-up. Visual stimulation always consists of flashes of 520 msec duration, with dark intervals of 520 msec. The intensity of these flashes was 4 asb. If the whole screen is illuminated this is called diffuse stimulation.

Data analysis

During the experiment all data consisting of the cell response, the EEG and the stimulus signal were stored on magnetic tape (Analog 7, Philips) and monitored by oscilloscopes. At the speed of the tape of $3\frac{3}{4}$ "/sec used, the bandwidth is 0 - 1250 cps. This bandwidth is too small to get an undistorted record of the shape of the spikes. Therefore for the analysis of this shape photographic records are made directly from the oscilloscope.

After the experiment the recorded data were analyzed. The response of the cell and the stimulus could be written on paper with a high frequency recorder (Oscillomink, Siemens) having a bandwidth of 0 - 1000 cps. The EEG and a signal giving the number of spikes per stimulus were recorded using a two-channel low frequency recorder (Sanborn 320). Time histograms of the spikes could be made with a signal averager (DRC, Nuclear Chicago).

Results

A unit in the LGN was searched during continuous diffuse stimulation of both eyes. Stimulus conditions were standardized as mentioned (flash intensity 4 asb, background intensity 1 asb, diffuse stimulation). When a unit was found, the eye which delivered no contribution to the response was covered. After plotting the receptive field of the unit with a small spot, an attempt was made to manipulate the electrode in a position in which a quasi-intracellular recording could be made, sometimes this happened spontaneously.

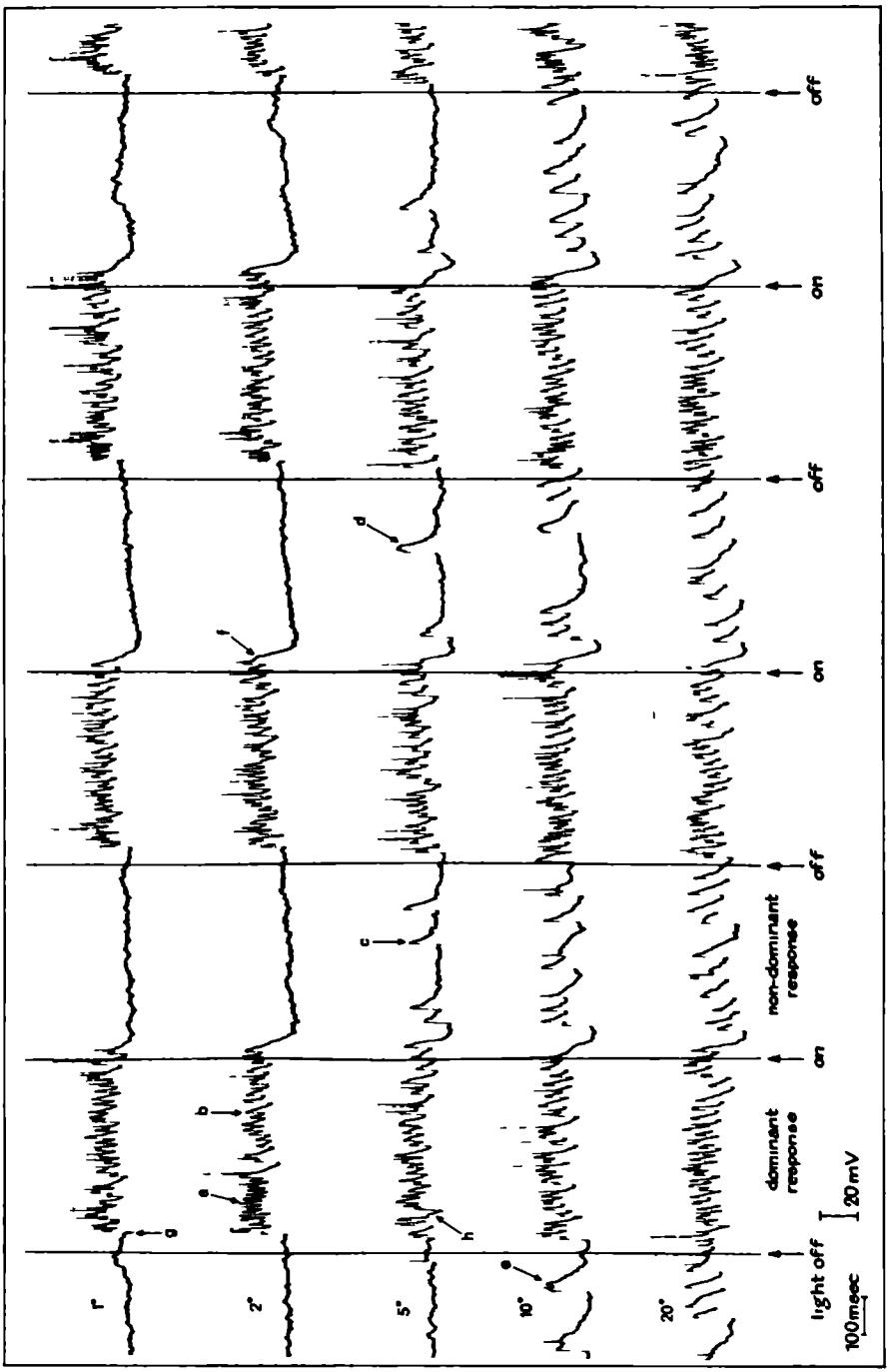
Quasi-intracellular recordings were made of 20 units. Most of them showed normal response characteristics and could be identified as ON-center OFF-surround or OFF-center ON-surround units (Hubel and Wiesel, 1961). The best record has been made of unit 65-2 an OFF-center unit. The responses of this unit to stimuli with different spot diameters are given in Figure 1.1. All phenomena, as spikes, subthreshold EPSPs and hyperpolarizations can be very clearly seen. For this reason this unit was very important in analyzing the characteristics of this type of recording. A number of other quasi-intracellular recordings are presented in Figure 1.2. For an analysis of this type of recording see also the papers of McIlwain and Creutzfeldt (1967) and Singer and Creutzfeldt (1970).

Excitatory phenomena

Spikes are mostly monophasic positive, sometimes followed by a small negative wave, indicating that the electrode is at some distance of the cell. The amplitude of the spikes of different units varies between 2 and 30 mV.

In unit 65-2 (Fig. 1.1) only a small part of the EPSPs generate a spike, many EPSPs are subthreshold. So there are two groups of EPSPs, the subthreshold EPSPs and the suprathreshold EPSPs which generate spikes. The EPSP part of these spikes can only be seen in the very first beginning of the spikes (Fig. 1.3). The transition from this EPSP to the steep slope of the spike is the so-called S-A inflexion (Bishop et al., 1962).

Subthreshold EPSPs have durations of 10 - 60 msec. In the dominant response period, as defined in the text of Figure 1.1, the durations of the EPSPs is 10 - 40 msec (Fig. 1.4a). From clear recordings (e.g. unit 65-2, Fig. 1.1; unit 75-4, Fig. 1.5) it can be seen that the EPSP duration


1'
2'
5'
10'
20'
a
b
c
d
e
f
g
h
light off
100msec
20mV
dominant response
non-dominant response
on
off

increases in the course of the response, on the average from 10 msec in the first part to 40 msec in the later part. The amplitude of the EPSPs in the first part of the response is also smaller, except the amplitude of the first one which is often extra large.

In the non-dominant response (Fig. 1.1) the duration (30 - 60 msec) and amplitude are on the average larger (Figs. 1.1 and 1.4a). A weak positive correlation exists between the amplitude and the duration of the EPSPs. Some observations suggest that a negative correlation exists between these EPSP characteristics and the level on which they begin. This was also noted by Coombs et al. (1955) for EPSPs of spinal cord units.

The 'delayed depolarizing potentials' (DDPs) described by McIlwain and Creutzfeldt (1967) could also be seen (Fig. 1.1) but we could not confirm their findings that these DDPs can generate clusters of spikes.

Figure 1.1. *(see opposite page).*
Responses of unit 65-2, an OFF-center ON-surround cell, to stimuli with different spot diameters as indicated on the left side of the Figure. According to Brooks and Bohn (1970) the response of an OFF-center ON-surround cell to light off and an ON-center OFF-surround cell to light on is called the dominant response, consequently the response of an OFF-center ON-surround cell to light on and an ON-center OFF-surround cell to light off is called the non-dominant response.

In general many subthreshold EPSPs are visible, the transfer ratio (see text) being about 0.4 in the dominant period and 0.2 in the non-dominant period in the case of large stimuli. Note the following characteristics, indicated by arrows and further described in the text.

a,b,c Subthreshold EPSPs showing different durations in different parts of the response.

d,e Delayed depolarizing potentials (DDPs).

f Beginning of the hyperpolarization in the non-dominant response. Note that no single IPSPs could be detected on the rising phase.

g,h Hyperpolarization in the dominant period at the beginning and during the response respectively.

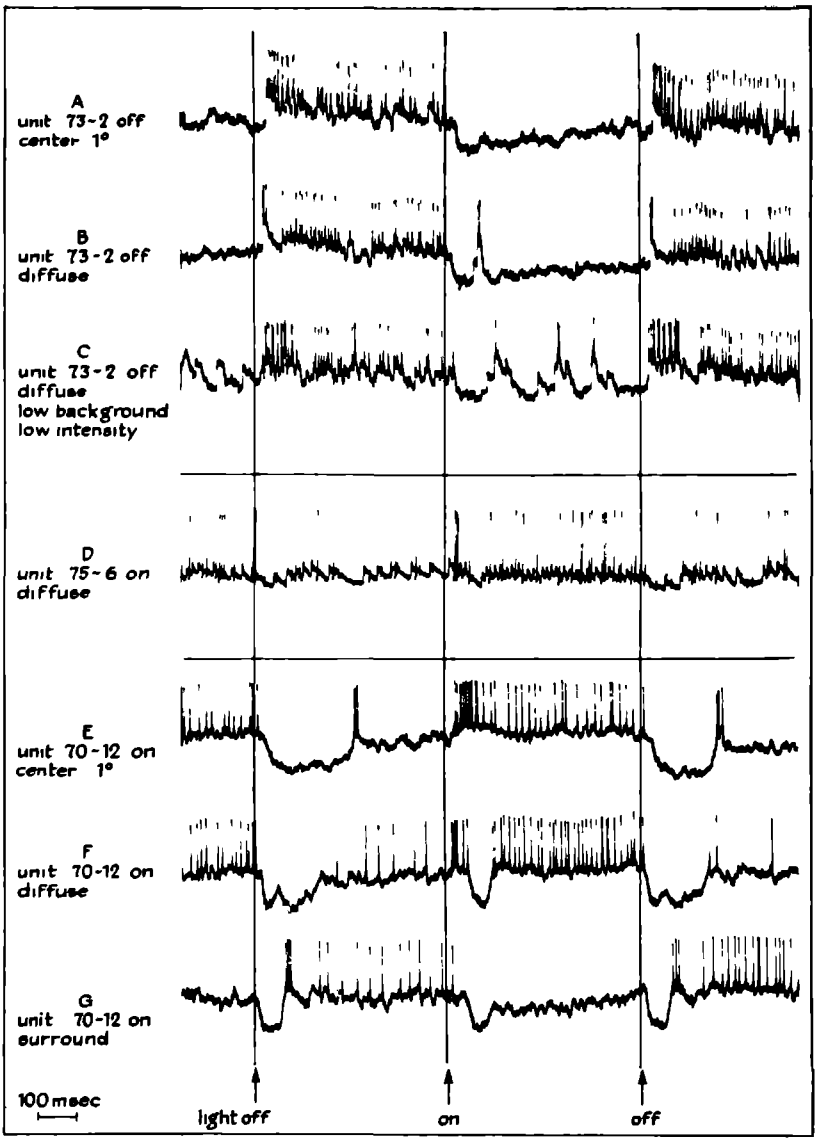


Figure 1.2 *Three examples of quasi-intracellular recordings.* A.B.C. *Unit 73-2, an OFF-center cell, stimulated as indicated in the Figure, shows many characteristics identical to those of unit 65-2. However, the transfer ratio of the dominant period is* 0.9 - 1.0. *In C the transfer ratio in the non-dominant period is about* 0.4, *which is low compared with the transfer ratio in the dominant period.*
D. *Unit 75-6, an ON-center cell, showing subthreshold EPSPs, but the hyperpolarizations are less clear.*
E.F.G. *Unit 70-12. Pronounced hyperpolarizations are visible but in this case the subthreshold EPSPs are difficult to see.*

The excitatory input of a unit

The question arises whether all incoming EPSPs are measured by an electrode in the quasi-intracellular recording position or that only some EPSPs are measured selectively, for example EPSPs incoming through one synapse or through one group of synapses occurring in a glomerulus as described by Szentagothai et al. (1966).

If we assume that 'invisible' EPSPs exist, these EPSPs can also reach the threshold and can generate a spike, but a spike generated by an invisible EPSP should lack the S-A inflexion. Consequently if all spikes show this S-A inflexion then all EPSPs are measured by the electrode. It appeared that all spikes showed the S-A inflexion (Fig. 1.3), and this

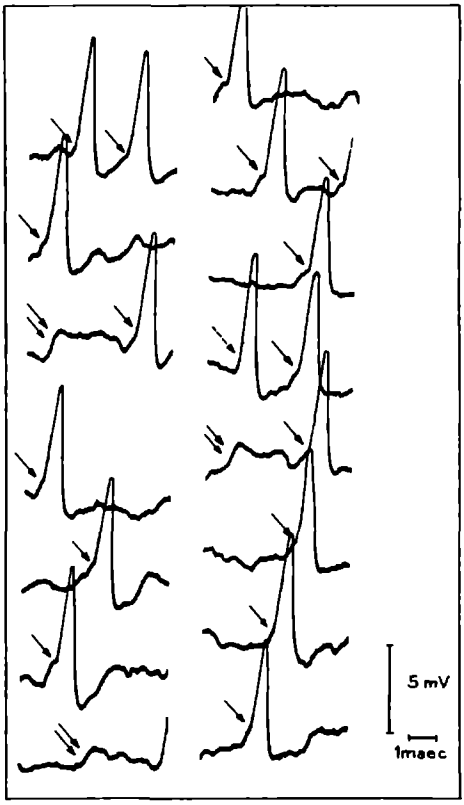


Figure 1.3 *Unit 76-3. Examples of quasi-intracellularly recorded spikes. The S-A inflexion is indicated by arrows, only in one case this notch is less clear (broken arrow). Some subthreshold EPSPs are indicated by double arrows.*

agrees well with the findings of Bishop et al. (1962). So the conclusion is drawn that the whole excitatory input is measured by an electrode in the quasi-intracellular recording position. The excitatory input consists of the total number of EPSPs being the total number of suprathreshold EPSPs or spikes added with the total number of subthreshold EPSPs. The output is simply the total number of spikes.

Now we can define a transfer ratio. This is the number of spikes per stimulus (output) divided by the total number of EPSPs per stimulus (input). Theoretically this transfer ratio can vary between zero, no EPSP is reaching the threshold and one, all EPSPs are reaching the threshold changing into spikes.

The origin of the excitatory input

It is generally accepted that all EPSPs are originating from optic tract fibres but it is still uncertain whether this excitatory input originates from only one optic tract fibre, as Creutzfeldt (1966) and Singer and Creutzfeldt (1970) state on the base of the uniform character of the EPSPs, or from more fibres as the histological findings suggest.

The EPSPs of our recordings show also this uniformity. In Figures 1.4a and 1.8 some amplitude distributions are given which are all unimodal. Although the time constants of the EPSPs cover a considerable range, as previously mentioned, not more than one group can be distinguished.

A second argument for a one fibre input is derived from the interval distribution of the input (Fig. 1.4b). The shortest intervals between the incoming EPSPs are about 2 msec. If there are inputs from more fibres then considerably shorter intervals could exist, but if only one input fibre exists then the shortest intervals are indeed about 2 msec, being the duration and the refractory period of a spike.

A third argument is that the spike frequency of optic tract fibres is on the average equal to the EPSP frequency of LGN neurons obtained from the quasi-intracellular recordings. This is pointed out in the following paper.

So little doubt remains about the statement that a geniculate neuron receives its input from one single optic tract fibre. This agrees with the findings of Hubel and Wiesel (1961) and Creutzfeldt (1968) that the receptive field characteristics of LGN cells are about the same as those of optic tract fibres.

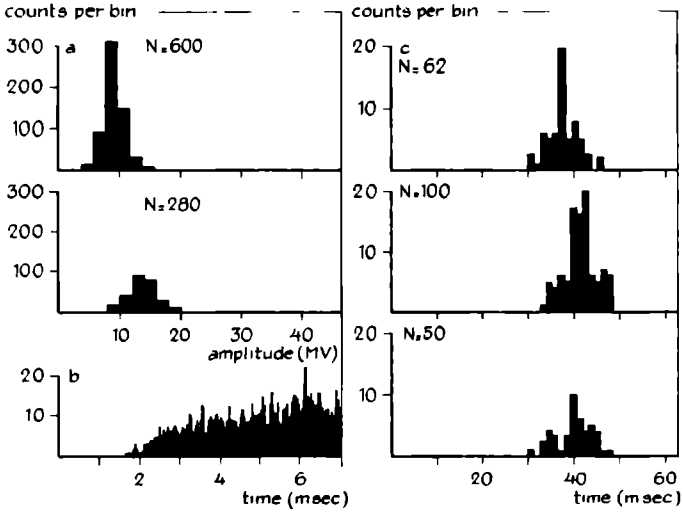


Figure 1.4 *Some characteristics of unit 65-2.*
a. Amplitude distribution of subthreshold EPSPs in the dominant period (above) and in the non-dominant period.
b. First part of the interval distribution of the input (subthreshold EPSPs and spikes).
c. Latencies of hyperpolarizations in the dominant period indicated by arrow g in Figure 1.1 (above), of EPSPs in the dominant response (middle) and of hyperpolarizations in the non-dominant period, indicated by arrow f in Figure 1.1 (below).

Inhibitory phenomena

After a latency of 30 - 40 msec the non-dominant response of an LGN unit to a small spot placed into the receptive field center starts with a prolonged hyperpolarization characterized by a rise time of 10 - 40 msec and a duration of about 200 - 300 msec (Fig. 1.1 arrow f and Fig. 1.2A). This long duration was also found by McIlwain and Creutzfeldt (1967), Singer and Creutzfeldt (1970) and Suzuki and Kato (1966). The amplitude of this hyperpolarization increases with increasing spot diameters, reaching a maximum when the whole receptive field is stimulated (Fig. 1.1). In this case the hyperpolarization seems considerably shorter, due to the fact that EPSPs, with a long latency, elicited by stimulation of the surround are

distorting the course of the hyperpolarization.

In the dominant response period ON-center cells show these pronounced hyperpolarizations after the first excitation, when the whole receptive field is stimulated (Fig. 1.2F). Mainly these hyperpolarizations find a clear expression in periods in which little EPSPs are arriving and the slow hyperpolarization is able to reach a low level. These silent periods are scarce in OFF-center cells and consequently the hyperpolarizations can only be recognized on their rising phases appearing as sharp negative peaks (Fig. 1.1 arrow h). These hyperpolarizations are present, even in responses elicited by stimulation of the center only.

In the response of unit 65-2 it can often be seen that the dominant response starts with such a negative peak (Fig. 1.1 arrow g). The latency of these peaks is, on the average, almost equal to the latency of the EPSPs in the dominant period and as the latency of the hyperpolarizations in the non-dominant period (Fig. 1.4c). The function of these hyperpolarizations will be treated in the Discussion, while the following paper is more concerned with the origin of these hyperpolarizations.

Influence of the level of consciousness on the transfer ratio

The transfer ratio, as defined previously, varies considerably for different units e.g. the transfer ratio for unit 65-2 is about 0.4 (Fig. 1.1) while this is about 1.0 for unit 73-2 (Fig. 1.2). According to the work of Maffei and Rizzolatti (1965) and Sakakura (1968) who described an increased responsiveness during wakefulness with respect to sleep, we correlated the transfer ratio with the level of consciousness of the animal. Indeed during the investigation of unit 65-2 the EEG showed a sleep pattern while during the investigation of unit 73-2 the EEG showed rather long periods of wakefulness. To test further this relation, we attempted to make a quasi-intracellular recording from a unit during different states of the animal. This was rather difficult for reasons described below but succeeded for three units (75-4, 76-3 and 79-7).

The investigation of unit 75-4 started when the cat was in a drowsy state. After a number of flashes the cat awoke spontaneously and returned to a drowsy state after some seconds. In this case a sleep state was artificially reached after induction of a light halothane anaesthesia for some minutes. The EEG of the cat showed in this period a clear sleep pattern. After termination of the anaesthesia the drowsy state was reached again after some minutes. The recordings made during

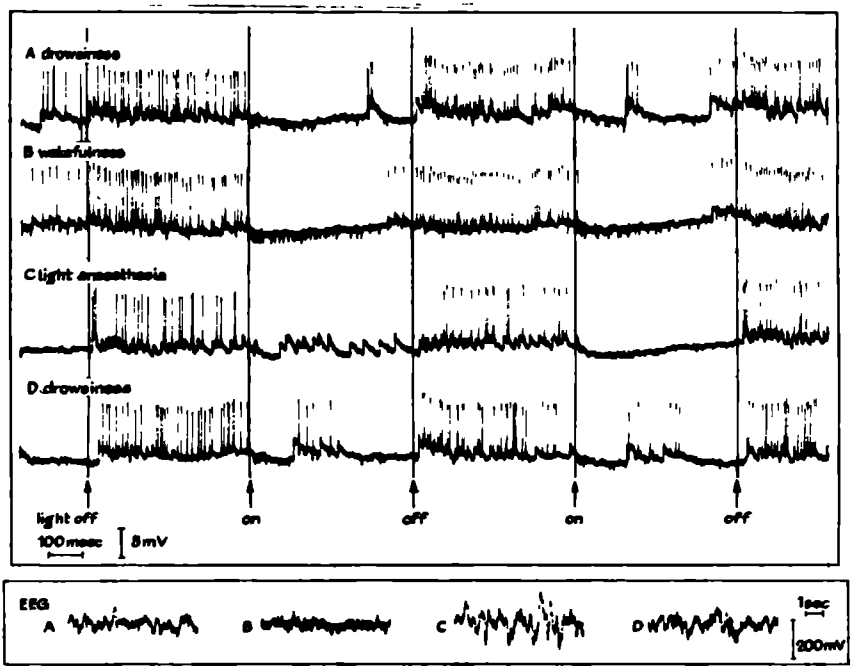


Figure 1.5 *Responses of unit 75-4, an OFF-center cell during different levels of consciousness of the cat, indicated on the left side of the Figure. The corresponding EEG is shown below. Note the behaviour of spikes and subthreshold EPSPs during the different states. Note also the behaviour of the small negative spikes (unit 75-4', an ON-cell) in the light on period. The numerical data are presented in table 1.1.*

state of the cat	unit 75-4				unit 75-4'
	number of spikes	number of subthreshold EPSPs	spikes + subthreshold EPSPs	transfer ratio	number of spikes
drowsiness	28 ± 3	10 ± 4	38 ± 3	0.75	20 ± 2
wakefulness . . .	40 ± 4	1 ± 1	41 ± 4	0.97	32 ± 3
light anaesthesia .	17 ± 4	20 ± 3	37 ± 2	0.46	10 ± 2
drowsiness	29 ± 4	11 ± 3	40 ± 2	0.71	18 ± 2

Table 1.1 *Numerical data of the responses of unit 75-4 and 75-4' (see Fig. 1.5). Data are taken from the dominant period of both units. Minimally 10 periods in every state were analyzed. Note the striking correspondence between the output (number of spikes) of both units.*

these different states are shown in Figure 1.5, the numerical data in table 1.1.

It was concluded that the input of unit 75-4 was rather constant while the output varied considerably depending on the state of consciousness of the animal. The transfer ratio increased from 0.5 during sleep or light anaesthesia, to 0.7 during drowsiness and further to about 1 during wakefulness.

The behaviour of unit 75-4', an ON-center unit recorded synchronously with unit 75-4 (Fig. 1.5, small negative spikes) is identical to the behaviour of unit 75-4 (table 1.1).

The units 76-3 and 79-7, presented in Figure 1.6, showed a similar pattern. The transfer ratio of unit 76-3 being 0.5 during sleep increased to about 1 when the EEG showed the alerted pattern. After a few seconds, the transfer ratio is decreased to 0.7 without a clear change in the EEG. In the further course of the experiment, which is not shown in the Figure, the transfer ratio varied between 0.7 and 1 while the EEG did not show any change. In unit 79-7 the transfer ratio increased from 0.4 to 0.7 when the cat changed from the sleep state into a more alerted state. Unfortunately the cell was damaged after some seconds.

It was often observed that a unit was damaged or lost if an arousal stimulus was given, mostly this arousal stimulus was given by pinching the cat's tail. The explanation might be that movements in the brain were induced, perhaps due to an increased heart beat or an increased blood pressure. Next to the difficulty in manipulating the electrode in the quasi-intracellular recording position, this damage or loss of the unit after an arousal stimulus was the second problem in these experiments.

The behaviour of the non-dominant response concerning the transfer ratio showed almost the same tendency as the dominant response. However, the transfer ratio is mostly lower (Figs. 1.1, 1.2 and 1.5). This point is discussed further on.

Comparison of activity of optic tract fibres with activity of LGN cells

Due to the inherent experimental difficulties, the number of quasi-intracellularly recorded cells during different states was rather small. Therefore the activity of a number of optic tract fibres was measured separately and compared with the activity of LGN cells. In Figure 1.7 such an experiment is shown. Unit 81-2 and unit 77-11 show the typical behaviour of an LGN neuron and an optic tract fibre respectively.

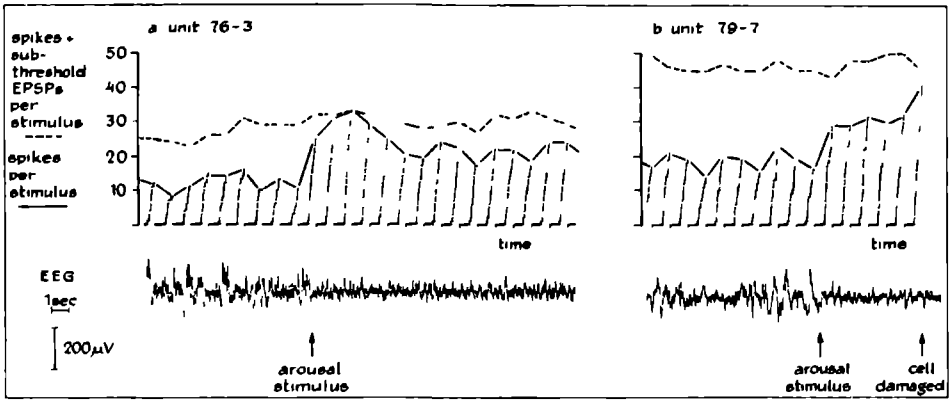


Figure 1.6 *Responsiveness to visual stimuli of two units (76-3, ON-center cell; 79-7, OFF-center cell). Upper line indicates the input (spikes and sub-threshold EPSPs), while the lower line indicates the output (spikes). Every vertical line represents the spike response to a stimulus. Only the response of the dominant period is considered in this Figure. In both cases the EEG desynchronizes after an arousal stimulus followed by a clear increase in responsiveness of the output, while the responsiveness of the input remains constant. Exceptionally the experiment of unit 79-7 was carried out at a background intensity of 0.01 asb, causing a rather high input frequency.*

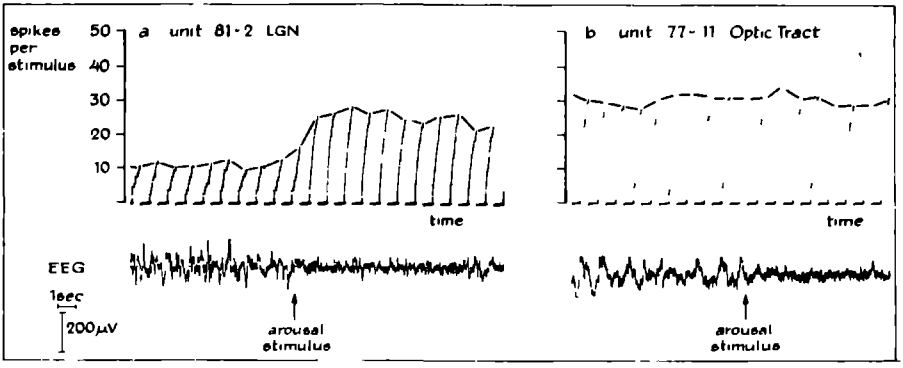


Figure 1.7 *A comparison between the responsiveness of an LGN unit (81-2, ON-center cell) and an optic tract unit (77-11, OFF-center unit). The responsiveness of the LGN unit clearly increases after desynchronization of the EEG while the responsiveness of the optic tract unit remains constant.*

Geniculate neurons show a clear increase in responsiveness if the EEG desynchronizes, while the responsiveness of optic tract fibres remains constant (Fig. 1.7). This is in full agreement with the results obtained from the quasi-intracellular recordings and with the results of Maffei and Rizzolatti (1965).

To complete this subject two final remarks. First, in some experiments several transitions from sleep to the alert state and vice versa could be obtained always showing the corresponding change in the responsiveness of LGN cells, and secondly, an ineffective arousal stimulus i.c. an arousal stimulus which has no effect on the EEG does not change the responsiveness.

The mechanism of the control of the transfer ratio

In order to get more information about the mechanism controlling the transfer ratio, the amplitude of the subthreshold EPSPs, present in the different states was measured.

The results from two units (75-4 and 79-7) are given in Figure 1.8. This Figure clearly shows that the amplitude of the subthreshold EPSPs increases from sleep to drowsiness.

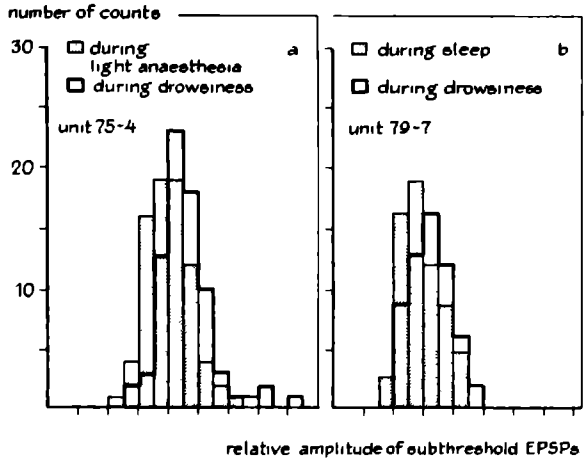


Figure 1.8 *Amplitude distributions of subthreshold EPSPs of two units (75-4 and 79-7). EPSP amplitude was measured in periods in which the spike amplitude was constant. Measurements were done in the dominant response periods only.*
The Figure clearly shows an increase of the amplitude of the subthreshold EPSPs in periods in which the level of consciousness is increased.

Unfortunately the amplitude of the subthreshold EPSPs cannot be measured reliably during the alert state, because their number is very small but it seems safe to extrapolate a further increase of the EPSP amplitude to the alert state.

So an increase of the EPSP amplitude is obviously responsible for the increase of the transfer ratio. Quantitatively this increase of the EPSP amplitude is estimated from about a value in the order of half of the threshold potential during sleep to at least the value of the threshold depolarization during wakefulness.

Discussion

It was found that all EPSPs elicited in an LGN neuron are measured by an electrode in the quasi-intracellular recording position. This was concluded from the fact that all spikes showed the S-A inflexion. There is a test on this conclusion, for if this is true, the relation between the number of spikes and the number of the subthreshold EPSPs must be linear with a regression line having a slope of minus one provided that the input is constant. Figure 1.9 shows that this relation is linear indeed, however, the slope of the regression line has a small deviation from the predicted value of minus one. This deviation can be explained by small fluctuations in the input activity or by a small amount of invisible input. This last explanation seems less probable but even if this is true the contribution of the invisible input to the measured input is so small that it may be neglected.

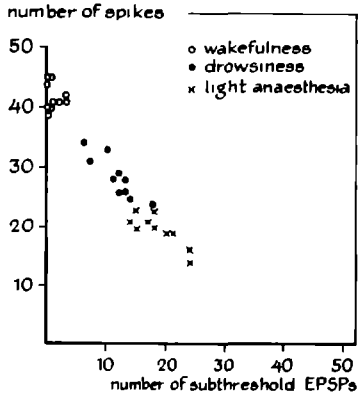


Figure 1.9 *Relation between the number of spikes and the number of subthreshold EPSPs of unit 75-4. This relation is linear, having a slope of about -0.8 to -0.9.*

In this paper evidence is given for the fact that all EPSPs are originating from one single optic tract fibre. Consequently there is no convergence in the LGN but only divergence and from the quantitative data of Bishop (1953) concerning the total number of optic tract fibres (125,000) and geniculate neurons (450,000), one can assume that, on the average, an optic tract fibre projects to 3 or 4 geniculate cells.

From histological data it is evident that one optic tract fibre splits in many terminals and projects with several synapses on a geniculate cell. Whether the electrode measures the summed activity from all these synapses or mainly from one synapse or from one group of synapses in the direct vicinity of the electrode tip is not clear, however, from functional point of view this is not important while all these synapses are originating from one fibre. The difference between cells concerning the ratio of the amplitude of EPSPs and hyperpolarizations, as is shown in Fig. 1.2 e.g. D and E, could then possibly be explained by a difference in location of excitatory and inhibitory synapses on the receiving neuron.

Transfer ratio

It is rather easy to see the functional significance of the control of the transfer ratio. The input determined by the retina does not change during sleep and wakefulness but the output, being the information for the visual cortex, is in the LGN modified according to the level of consciousness of the animal. During sleep the activity to the visual cortex is considerably reduced and one can imagine that such a reduction of inflowing sensory activity is necessary for the physiological process of sleep. During wakefulness all information is important and is, in this state, entirely transmitted to the visual cortex. Drowsiness is an intermediate state, somewhat difficult to recognize on the EEG, but it seems that the amount of information reaching the higher centers is also intermediate between sleep and wakefulness.

With these findings it is also easy to understand why the receptive field of LGN neurons increases if the animal is alerted as described by Meulders and Godfraind (1969). The small optic tract responses originating from peripheral parts of the retinal receptive fields are mainly blocked during sleep, but during arousal these responses are fully transmitted.

The transfer ratio of a unit is mainly determined for the dominant response period of a unit. During the non-dominant period, in which the surround predominates, the transfer ratio is often lower in the same state of consciousness of the animal. This is mainly due to two facts. First the summation effect of the EPSPs is smaller, due to the mostly lowered firing frequency of the unit in the non-dominant period, and second the EPSPs often start from a lower level, due to the initial hyperpolarizations in these periods. In spite of the somewhat increased amplitude of the EPSPs, they reach the threshold more difficult. The suppression of the activity in these periods could have physiological significance. More data will be given in the following paper.

The hyperpolarizations appearing in the dominant response period can suppress some EPSPs, but the influence on the transfer ratio of the whole period is small, therefore the physiological significance of the hyperpolarizations in this period is rather doubtful.

In general the transfer ratio is mainly controlled by a mechanism which is able to change the amplitude of the EPSPs, possibly regulated by the reticular formation. The control of the size of the EPSPs can happen through presynaptic inhibition or by changing the excitability of the postsynaptic neuron.

For the last possibility literature data provide little evidence, only some measurements of evoked potentials are in favour of these postsynaptic changes (Iwama et al., 1966; Malcolm et al., 1970). These measurements, however, are difficult to interpret.

The data suggesting the existence of presynaptic inhibition in the LGN are more numerous and more clear (Iwama et al., 1966; Angel et al., 1965; Kahn et al., 1967; Suzuki and Kato, 1965; Pecci-Saavedra and Wilson, 1965). Indeed a mechanism working like presynaptic inhibition might be a good explanation of the findings described in this paper. However, the axo-axonal synapses of the right polarity necessary for this presynaptic inhibition could not been found in the LGN (Szentagothai et al., 1966). But as Szentagothai et al. (1966) state, the neuronal connexions in the LGN glomeruli are so numerous and are so closely packed that it is difficult to reach a definite conclusion.

Summary

1. Quasi-intracellular recordings from neurons in the lateral geniculate nucleus of the cat have been made. From these recordings the excitatory input of these neurons could be determined.

2. The experiments suggest that the excitatory input of a geniculate neuron is originating from one single optic tract fibre.

3. The experiments were performed on non-anaesthetized paralyzed cats which showed different levels of consciousness as sleep, drowsiness and wakefulness. During these different levels the input of the geniculate neurons remains constant but the output varies considerable.
The transfer ratio, defined as the ratio between the spike frequency (output) and the EPSP frequency (input) of a neuron is high (0.9 - 1.0) during wakefulness and low (0.4 - 0.5) during sleep with intermediate values at intermediate states.

4. The control of the transfer ratio is caused by changing the amplitude of the EPSPs. During wakefulness nearly all EPSPs reach the threshold; during sleep the EPSPs are smaller than the threshold potential. A mechanism working like presynaptic inhibition is presumably responsible for the change of the EPSP amplitude.

5. The control of the flow of information to the visual cortex according to the level of consciousness is probably one of the functions of the lateral geniculate nucleus.

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CHAPTER 2

ANALYSIS OF THE RESPONSE CHARACTERISTICS OF OPTIC TRACT AND GENICULATE UNITS AND THEIR MUTUAL RELATION

Introduction

In a previous paper responses of neurons in the lateral geniculate nucleus (LGN) of the cat were analyzed in relation to the level of alertness of the cat. Mainly the responsiveness, expressed in the number of spikes occurring during a stimulus period, was used as a parameter (Chapter 1).

In the present paper more details of the responses will be given. The responses are described using various response characteristics. The behaviour of these characteristics to some important stimulus parameters such as the background intensity, the size of the stimulus spot and the level of alertness of the cat, were investigated.

The responses of the optic tract fibres were measured in the same way. The behaviour of the response characteristics were studied just as was done for the LGN units. On the basis of a comparison of the responses of the two levels it could be established which characteristics of the LGN units could already be found on the optic tract level. Furthermore the analysis of the optic tract responses gives rise to considerations about the importance of the latency to the first excitation. This led to some conclusions about the sizes of the retinal receptive fields. Comparison between the optic tract and geniculate responses seemed the more attractive because evidence exists that a geniculate neuron receives its main excitatory input from one optic tract fibre only (Singer and Creutzfeldt, 1970; Chapter 1). A comparison of the optic tract responses with the input responses of geniculate neurons, obtained by means

of the quasi-intracellular recordings further confirmed this point.

It appeared that all differences between the optic tract and geniculate responses were of an inhibitory nature. As well as a considerable difference in responsiveness, caused by the fact that most recordings were done when the cat was asleep (Chapter 1), some differences exist which were due to the influence of the intrageniculate hyperpolarizations. The origin of these hyperpolarizations is discussed in relation with the work of Burke and Sefton (1966a, b, c) and Singer and Creutzfeldt (1970).

A brief report of this work has been presented previously (Coenen et al., 1971).

Methods

The experiments were carried out simultaneously with the preceeding series of experiments (Chapter 1). In general the same methods were used.

The cats, which were non-anaesthetized and paralyzed, faced a screen at a distance of 57 cm on which visual stimuli, consisting of series of alternating light-on and light-off periods of 520 msec each, could be given. Mostly these stimuli had an intensity of 4 asb, while the background intensity was 1 asb.

Responses of single units were recorded with glass micropipettes in the optic tract just behind the optic chiasma and in the LGN. Responses were recorded on magnetic tape and analyzed later. Spikes were converted, using a level detector, into standard pulses which were stored in digital form on DEC-tapes of a PDP-9 computer. The computer was programmed to construct time histograms and dot-displays and to calculate a number of numerical values of the responses. Post Stimulus Time Histograms (PSTHs) with a binwidth of 2.5 msec, were always made by averaging 50 stimuli.

In some cases it was possible to make a PSTH of the input of an LGN unit (Chapter 1). The level detector was then adjusted in such a way that both the spikes and the subthreshold EPSPs were transmitted and converted into standard pulses.

Results

All optic tract units (46) were identified as ON-center OFF-surround units (24) or OFF-center ON-surround units (22).

In total 97 LGN units were analyzed, 43 appeared to be ON-center OFF-surround units and 44 OFF-center ON-surround

units. The remaining 10 LGN units showed variable characteristics.

Most units were situated in the central area of the retina.

Characteristics of optic tract and geniculate responses

The comparison between the responses of optic tract and LGN units was made for a number of response characteristics named according to the terminology of Singer and Creutzfeldt (1970) for LGN cells. In Figure 2.1 some of these characteristics are indicated in the PSTH of a typical ON-center unit. All

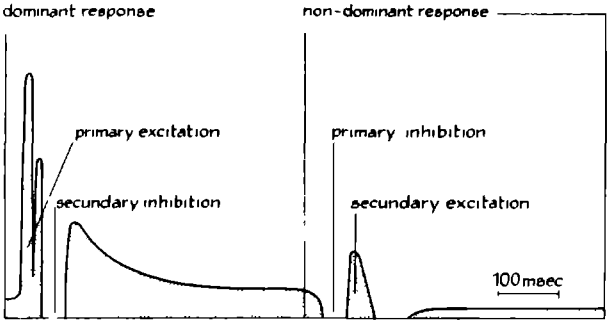

Figure 2.1 Schematic PSTH of a typical ON-center unit. Some response characteristics described in the text.

characteristics hold for ON-center as well as OFF-center units of both levels.

Responses were divided into two parts, the dominant response being the response to light-on for an ON-center unit and the response to light-off for an OFF-center unit, and the non-dominant response being the response to light-off for an ON-center unit and the response to light-on for an OFF-center unit.

The general response behaviour to a diffuse stimulation in the light adapted state could be described as follows. After a short latency of about 30 msec the dominant response mostly starts with a short high frequency burst of spikes, called the primary excitation. This excitation, lasting up to about 60 msec, is followed by a fast decrease in the spike frequency, often leading to a complete firing pause. This is called the secondary inhibition. The duration of this inhibition is variable but the bulk of the inhibition occurs at about 80 msec. Hereafter this excitation increases again and after some fluctuations a constant activity is reached in 200 to 400 msec, this is called the maintained activity. The non-dominant response starts again,

after a short latency, with an inhibition called primary inhibition followed by an excitation, the secondary excitation having a long latency of about 70 msec, whereas maintained activity is again reached after 200 to 400 msec. The total number of spikes in both periods is used as a measure for the responsiveness to the stimulus.

In order to asign a magnitude to these quantities more exact definitions must be given. The following definitions seemed the best choice to us.

In the dominant response period:

- latency. The time in milliseconds between stimulus onset and the point of reaching half of the top value of the PSTH.
- primary excitation. The maximal firing frequency of the response between 10 and 75 msec. This corresponds with the top value of the PSTH.
- secondary inhibition. This is determined on the base of the shape of the PSTH. A clear firing pause after the primary excitation was interpreted as a strong inhibition (e.g. unit 78-11, Fig. 2.5); a dent in the PSTH after the primary excitation, accompanied by an oscillating firing pattern, as a moderate inhibition (e.g. unit 82-6, 80-6, Fig. 2.6); while a regular decreasing transient was interpreted as a weak inhibition or an absence of inhibition (e.g. units 83-5, 77-4, Figs. 2.5 and 2.6).
- maintained activity. The mean firing frequency in the period between 400 and 500 msec.
- responsiveness. The total number of spikes per stimulus in the dominant response period.

In the non-dominant response period:

- latency to primary inhibition. Time in milliseconds between stimulus offset and the point at which the activity is decreased by 50%.
- latency to secondary excitation. Time between stimulus offset and the point of reaching 50% of the top value of the secondary excitation.
- secondary excitation. Maximal firing frequency of the activity in the time between 40 and 150 msec.
- maintained activity. The mean firing frequency in the period between 400 and 500 msec after stimulus offset.
- responsiveness. The total number of spikes per stimulus in the non-dominant response period.

General identification of the response characteristics

To obtain a good insight into the relation of these characteristics with stimulus parameters, the influence of changes of some important parameters on the response was studied.

Influence of spot size

It is well known that a response to a diffuse stimulation is achieved by an interaction between the activities of the two antagonistic parts of the receptive field, the center and the surround. In general optic tract units have receptive fields with a center mostly circular in shape and a surround lying around the center. The size of the center ranges from about 0.5° to 2° in the central part of the retina to about 4° in more peripheral parts (Kuffler, 1953; Wiesel, 1960; Rodieck and Stone, 1965). The surround extends up to about 8 - 12°, (Kuffler, 1953; Wiesel, 1960) but its outer boundaries are difficult to determine.

Geniculate receptive fields closely resemble the optic tract receptive fields (Hubel and Wiesel, 1961). In order to distinguish between the response characteristics originating from the center and the surround, the receptive field was stimulated with circular spots of different diameters. In Figure 2.1 the typical behaviour of an optic tract ON-center and an OFF-center fibre is shown, while in the previous paper some examples of quasi-intracellular responses of LGN units to this type of stimulation are presented (Chapter 1).

The results of these experiments, which mainly agree with what could be expected on the basis of the results of e.g. Wiesel (1960), Hubel and Wiesel (1961), Rodieck and Stone (1965) and Singer and Creutzfeldt (1970) could be summarized as follows. The primary excitation and inhibition are responses of the center, always having short latencies. These latencies decrease from about 50 msec to 20 - 30 msec if the spot size increases from 1° to 20°. The secondary inhibition and excitation are responses of the surround. These activities always have longer latencies compared with the latencies of the center (about 50 to 150 msec) which is due to the conduction time of the surround activities in the extra lateral path (Wuttke and Grüsser, 1965). So based only on the latencies of the primary and secondary excitation one can establish whether the response is originating from an ON-center or an OFF-center unit.

In doing these experiments with increasing spot diameters

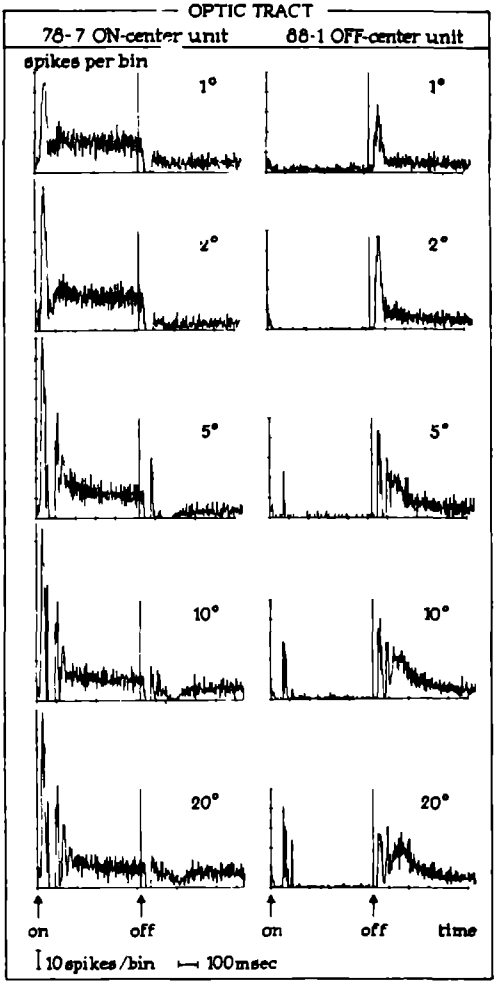

Figure 2.2 *Responses of a representative optic tract ON-center and OFF-center fibre to stimulation with circular spots of increasing diameters. Spots were centered to the receptive field center. Background intensity was 1 asb. Spot intensity 4 asb and constant per unit of area. Spot diameter is indicated at every PSTH. Note the increasing influence of the surround, expressed in an increased secondary inhibition in the dominant and an increased secondary excitation in the non-dominant response period. Note also the decreasing primary excitation of the OFF-center units from 5° up to 20°. Exceptionally in these experiments the eyes of the cat were corrected with contact lenses.*

it appeared that the behaviour of ON-center and OFF-center characteristics was not identical. Response characteristics of ON-center units generally do not change further when the receptive field is stimulated with a spot greater than 5° - 10°, while OFF-center units still show some characteristic changes to stimulation with a spot of up to 20° (Figs. 2.2 and 2.7). ON-center units show mostly a strong center of about 2° and a strong surround lying mainly between 2 and 10 degrees (Fig. 2.2). The receptive fields of OFF-center units, on the other hand, are less sensitive, as indicated by the low responsiveness of the OFF-center units to a spot of one degree (Fig. 2.2), and more extended. The latency to the primary excitation still shortens considerably between 5 and 20°, while also other characteristics undergo further changes in this range (Figs. 2.2 and 2.7). These changes are described and discussed further on. The behaviour of these characteristics indicate that the receptive field is extended between 10 and 20 degrees.

The behaviour of geniculate neurons to stimulation with spots of different diameters is qualitatively similar to that of optic tract units. General differences between ON- and OFF-center units as established for tract units also exist on this level.

Influence of the background intensity

From the work of Barlow et al. (1957) it is already known that the surround of the receptive field is inactive in the dark adapted state of the cat. In our investigation we had no intention to measure the response characteristics in a fully dark adapted animal, but we were only interested how characteristics would behave as a function of the background intensity. Therefore the following experiment was performed. Starting from a low level background intensity (0.01 asb), on which the cat was adapted for some minutes, the background intensity was slowly raised by increasing the voltage of the bulb of a projector shining on the whole screen of the visual stimulator. During this increase the responses to flashes with a fixed intensity were measured. In Figure 2.3 the results for an OFF-center optic tract and an ON-center LGN unit are shown.

Indeed it appeared that, on raising the background intensity, both the secondary excitation and inhibition are increased, while the primary excitation and the maintained activity in the dominant response are decreased. This indicates an increasing activity of the surround with increasing background

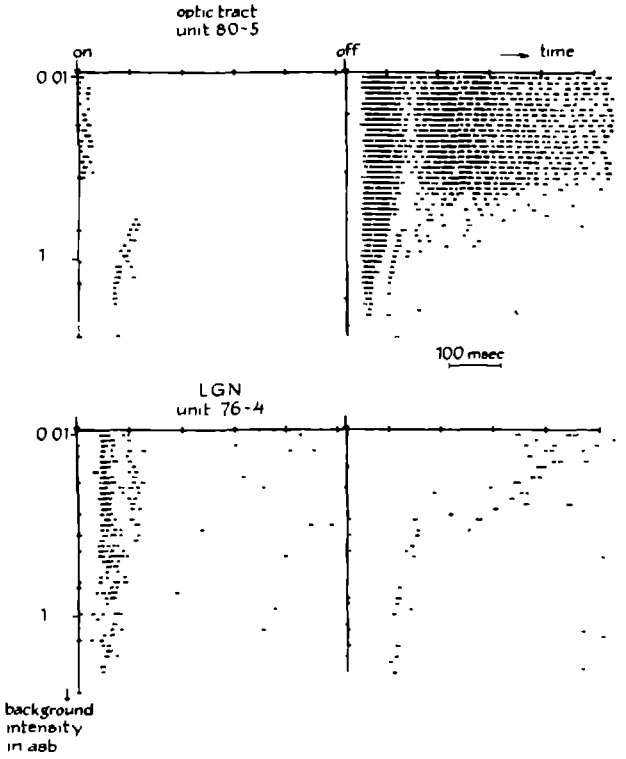

Figure 2.3 *Dot-displays of the responses of an optic tract OFF-center unit and an LGN ON-center unit at increasing background intensity. Each horizontal line gives the response at a background intensity which is roughly indicated at the ordinate. Each spike is represented as a dot. Stimulus intensity 4 asb, diffuse stimulation.*

intensities. Figure 2.3 clearly shows the antagonistic behaviour of the dominant and non-dominant responses. Note in this Figure the considerable shortening of the latency to the secondary inhibition in the dominant period and the corresponding secondary excitation in the non-dominant period while the latency of the primary excitation is hardly changed.

Finally, some remarks must be made concerning the responses of optic tract units under low background intensity (0.01 asb). At most OFF-center units and about 30% of the ON-center units the secondary activities originating from the surround are almost abolished. The other ON-center units, mainly those with

a high primary excitation and strong secondary activities in the light adapted state (see later) indeed show decreased secondary activities which, however, are still appreciable.

The behaviour of geniculate response characteristics is about the same. A minor difference is that at the geniculate level the presence of the secondary inhibition in the ON-center units is generally clearer.

The paper of Brooks and Bohn (1970) presents more quantitative data about the responses of optic tract and geniculate neurons during different background intensities.

Influence of the level of alertness

As shown by Maffei and Rizzolatti (1965) and in the foregoing paper (Chapter 1) conditions of sleep and wakefulness do not influence the optic tract responses, but geniculate responses are sensitive for changes in the level of alertness. Responses made during wakefulness approximate to the optic tract responses.

A nitrous oxide anaesthesia, recently used by many investigators, mostly induces a state which is comparable to the state of sleep as judged by the EEG. In agreement with this finding nitrous oxide does not cause any changes on the optic tract level, whereas on the geniculate level the responses are similar to those made under sleep (Fig. 2.4).

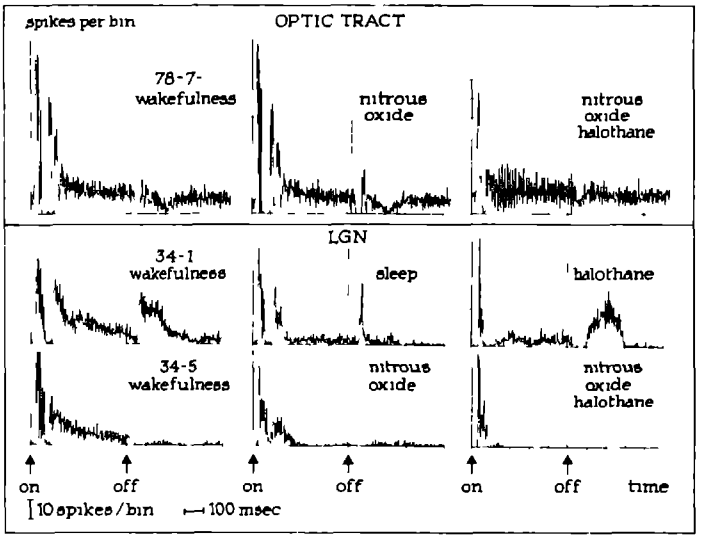

Figure 2.4 *The influence of the level of alertness on the responses of OT and LGN units. In these experiments anaesthetics were added to the ventilation gas, about 25% nitrous oxide (with 75% oxygen) and about 1% halothane were given.*

Using a strong clinical anaesthetic such as halothane, both the optic tract and geniculate responses are influenced (Fig. 2.4). On the optic tract level the responsiveness is almost constant but the interval distribution is changed. This could be seen even in the PSTH (see Fig. 2.4, unit 78-7). The changes on the geniculate level are more remarkable (Fig. 2.4). The response activity is mostly very low, often the unit fires with only a small burst of spikes to a stimulus. In one case we observed, however, that the secondary excitation was increased.

From these results it was concluded that in both quantitative and qualitative respects such an anaesthetic is undesirable in the experiments, particularly for measurements on LGN or a more central level. A nitrous oxide anaesthesia, however, can safely be used in measurements on the optic tract and LGN level. In the latter case one must realise that the responses are comparable to those made during sleep.

Comparison between optic tract and geniculate responses

ON-center OFF-surround units

Responses of optic tract and geniculate units were compared on the basis of their characteristics shown in the PSTHs. A number of these time histograms from both levels is shown in Figure 2.5, whereas the numerical values of the response characteristics are presented in table 2.1. About 70% of the PSTHs of ON-center units show the pattern as seen in the upper row of Figure 2.5, with a high primary excitation, a strong secondary inhibition and a moderate secondary excitation.

The remaining 30%, presented in the second row, show a lower primary excitation and no, or a weak, secondary inhibition and excitation. This might indicate a different interaction of center and surround in these units (Jacobs and Yolton, 1970). Still there are no separate groups of units, witness the fact that there is a continuous transition between the response patterns with a strong and a weak excitation and inhibition.

Geniculate responses, which are presented in the lower two rows of Figure 2.5, show a considerable reduction in the responsiveness to visual stimuli (table 2.1). This is expressed in decreased primary excitations with increased latencies and in decreased maintained activities. In general the responsiveness of geniculate neurons is a factor of twofold lower than that of optic tract fibres (see also Creutzfeldt, 1968). A second difference from the responses of optic tract fibres is that

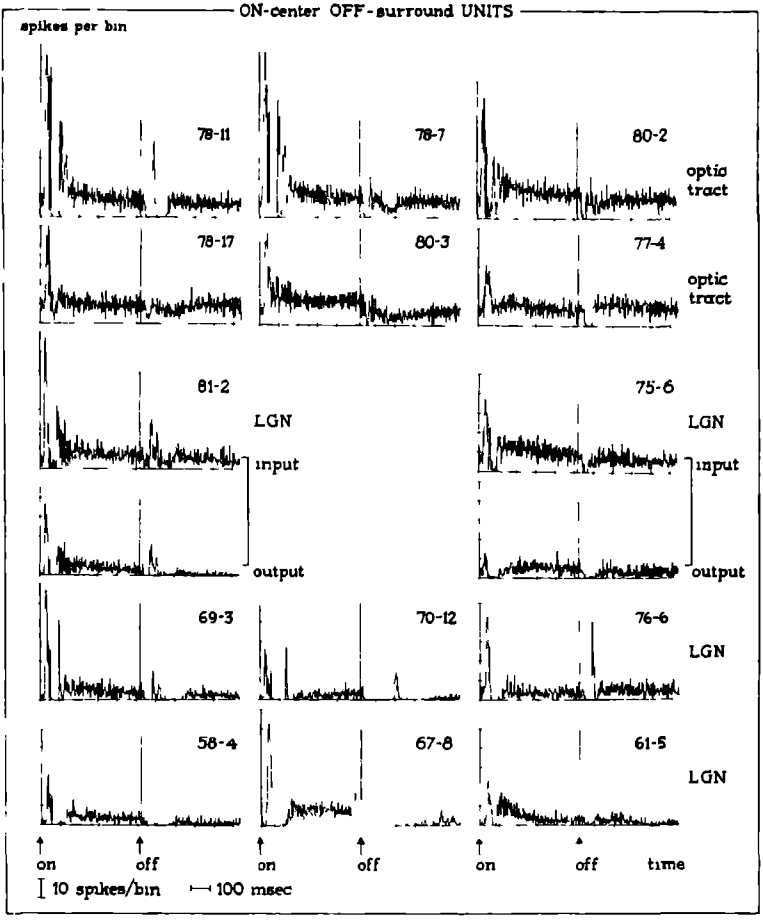

Figure 2.5 PSTHs of optic tract and geniculate neurons. Diffuse stimulation, stimulus intensity 4 asb, background intensity 1 asb. Upper two rows show optic tract responses and lower two rows lateral geniculate responses. In the middle rows input-output relations of two LGN-units are presented. Note the close similarity between the input histograms of LGN-units and the optic tract PSTHs. All PSTHs are composed of 50 sweeps.

Table 2.1 *Numerical values of response characteristics of optic tract and geniculate responses. Values of the averages and standard deviations of response characteristics of optic tract and geniculate responses.*

ON-center OFF-surround units

	Optic tract	LGN input	LGN output
number of units	24	2	43
Dominant response			
latency (prim. exc.)	27 ± 3	26	29 ± 6
primary excitation	450 ± 164	416	344 ± 129
secondary inhibition	+/-	+/-	±
maintained activity	77 ± 19	66	34 ± 20
responsiveness	51 ± 11	41	24 ± 11
Non-dominant response			
latency (prim. inh.)	27 ± 7	30	25 ± 8
latency (sec. exc.)	64 ± 16	57	78 ± 19
secondary excitation	178 ± 76	156	170 ± 139
maintained activity	62 ± 15	44	25 ± 16
responsiveness	32 ± 7	24	14 ± 9

OFF-center ON-surround units

	Optic tract	LGN input	LGN output
number of units	22	3	44
Dominant response			
latency (prim. exc.)	29 ± 6	32	31 ± 10
primary excitation	276 ± 108	227	208 ± 90
secondary inhibition	+/-	+/-	+/-
maintained activity	23 ± 18	34	20 ± 19
responsiveness	24 ± 13	26	17 ± 9
Non-dominant response			
latency (prim. inh.)	20 ± 6	30	22 ± 7
latency (sec. exc.)	68 ± 10	70	85 ± 15
secondary excitation	247 ± 98	195	135 ± 106
maintained activity	11 ± 13	14	9 ± 9
responsiveness	11 ± 8	10	6 ± 4

all geniculate ON-center neurons show a strong secondary inhibition. This means that optic tract responses without secondary inhibition are changed in such a way that a secondary inhibition arises on LGN level.

A third difference is that the activity in the non-dominant response period is more suppressed on the LGN level than the activity of the dominant response period in the transfer of the optic tract activity. This is not clear from table 2.1, which is due to the great variability in the responsiveness of the LGN units. When the dominant and non-dominant responses of each unit are compared separately, about 60% of the non-dominant LGN responses are more suppressed than the dominant LGN responses. In the first 100 to 200 msec especially the first activity is strongest suppressed. This is clearly visible in some quasi-intracellular recordings (see Chapter 1). From these recordings it was clear that the intrageniculate hyperpolarizations were responsible for this extra-suppression of the activity.

OFF-center ON-surround units

In Figure 2.6 a number of both optic tract and geniculate PSTHs are presented, whereas table 2.1 again shows the averaged numerical values of the response characteristics. The OFF-center units form a rather variable group. Typical responses are 82-6 and 83-5.

Generally the characteristic OFF-center histogram deviates from ON-center histograms. OFF-center units show mostly a moderate primary excitation and a weak secondary inhibition (Fig. 2.9). Maintained activity and responsiveness are highly fluctuating, secondary excitation is generally present. Rather slowly and rather quickly adapting units occur, e.g. units 80-6 and 78-9 respectively (Fig. 2.6).

Latency to the primary excitation is about 30 msec, which is identical to the latency of the primary excitations of ON-center units. In contrast the latency to the primary inhibition is very short (about 20 msec). This surprising behaviour of the latency of the primary inhibition of OFF-center units was found earlier by Freund et al. (1970).

Responses of geniculate units resemble closely the optic tract responses. Responsiveness of geniculate neurons is somewhat lower whereas the extra suppression of the responsiveness of the non-dominant response period also could often be seen (see Chapter 1, Fig. 1.1, unit 65-2). However, probably the differences between optic tract and geniculate units will be greater than table 2.1 shows. This will be due to the fact

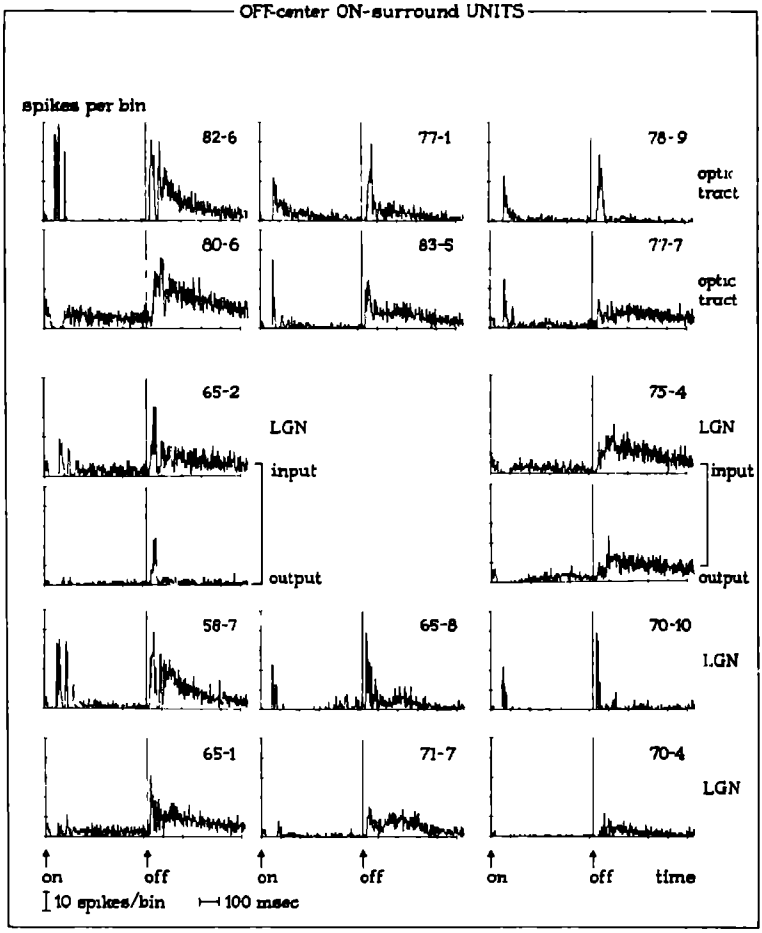

Figure 2.6 PSTHs of OFF-center ON-surround units of optic tract (upper two rows) and geniculate units (lower two rows). In the two middle rows some input-output relations of LGN-units are shown. All PSTHs are again constructed by averaging 50 sweeps.

that OFF-center tract units under these stimulus conditions, in contrast with ON-center units, sometimes show a very low responsiveness. It is likely that these units might be neglected on geniculate level, particularly when the transfer ratio of the geniculate neurons is low.

Input histograms of geniculate neurons

In 5 cases (2 ON-center units, 3 OFF-center units) it was also possible to construct a PSTH of the input, consisting of the spikes and subthreshold EPSPs of the response obtained by means of the quasi-intracellular recordings. The shape of these time histograms (Figs. 2.5 and 2.6 middle rows) as well as the numerical values of the response characteristics (table 2.1) clearly indicate that these input responses are statistically equal to the optic tract responses. This is again a strong argument for the assumption based on data of Singer and Creutzfeldt (1970) and Chapter 1 that a geniculate neuron receives its main excitatory input from one optic tract fibre. So the arguments for a one fibre input to geniculate neurons are now so strong that, although it is dangerous to generalize, it must be true in relatively many cases.

Consequently, an optic tract response often represents the direct input of a geniculate neuron which means that the transfer characteristics of geniculate neurons could be analyzed more or less by comparing the optic tract and geniculate responses.

The input-output relations of geniculate neurons, obtained from the quasi-intracellular recordings, confirm the results obtained from comparison of the responses of the two levels. The quasi-intracellular recordings show also that, as mentioned, the differences such as the extra suppression of the activities in some periods are originating from the existence of intra-geniculate hyperpolarizations.

When this paper was written an article of Cleland et al. (1971) concerning the same problem was published. In recording simultaneously from corresponding geniculate and ganglion units they found that in 50% of cases the LGN unit receives its main excitatory input of one single optic tract fibre, while in the remaining 50% two or sometimes three optic tract fibres project to an LGN unit.

Discussion

Latency as a parameter for the excitatory receptive field of tract units

A generally accepted idea in neurophysiology is that the latency decreases when the activity increases. This is also the case when the receptive field of an ON-center neuron is stimulated with spots of increasing diameters. Generally the latency decreases while the primary excitation increases (Fig. 2.7). However, most OFF-center units show variable results. Initially primary excitation increases accompanied by a decrease in latency but when stimulated with larger spots the primary excitation diminishes while the latency increases further (Fig. 2.7). The only explanation of this remarkable

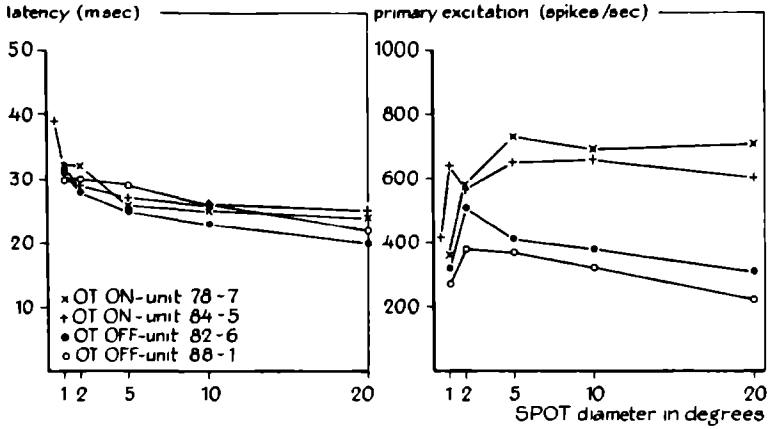

Figure 2.7 *Graph showing the relation between the latency of the primary excitation and the spot diameter (left) and the primary excitation and the spot diameter (right).*
Note the differences between optic tract ON-center units and OFF-center units.

phenomenon seems to be that the original retinal excitation elicited by the stimulus increases, but is diminished by an increasing surround inhibition so that the net excitation, measured as the primary excitation, decreases. This implies that the latency is determined by the excitation before the inhibition is affecting it.

Consequently the conclusion must be that the latency to the primary excitation is a more reliable parameter for

the original excitation elicited by the stimulus than the primary excitation itself which is determined by excitation and inhibition together.

Confirmation of this conclusion is suggested by the behaviour of the latency to the primary excitation when the background intensity is increased (Fig. 2.3). The secondary inhibition elicited by the surround increases, which is responsible for the decrease of the primary excitation. In fact the original excitation elicited by the stimulus does not change which agrees with the fact that the latency to the primary excitation is also constant.

On the basis of the latency as parameter of the excitation, the size of the excitatory receptive field could be determined from the experiments with increasing spot diameters. As soon as the latency reaches an almost stable level the excitatory receptive field is completely stimulated. As can be seen in Figure 2.7 the latency to the primary excitation of ON-center units increases with spot sizes up to 5^{o}, which means that their excitatory receptive fields are mostly not larger than 5^{o}.

On the other hand the latency of the primary excitation of most OFF-center units decreases with spot sizes up to 20^{o}. In the area of 5^{o} to 20^{o} the latency decreases with 5 msec or more which corresponds to the presence of a rather strong excitation in this area (Fig. 2.7).

Fischer and May (1970) and Fukada (1971) also found that the sizes of the receptive field centers of OFF-units were larger compared with ON-units. Both observations were based on plotting the field with a small spot. However, their differences between ON- and OFF-units were small. This could be explained by assuming that the small excitation elicited by a small spot in the far peripheral parts is fully cancelled by the inhibition. In using our method with the increasing spot diameters a large area of the peripheral parts is stimulated synchronously leading to a considerable decrease in latency.

We tried to quantitatively correlate the latency with the amount of original excitation, which also implies that the original inhibition should be known. The idea was that we obtained a response with only excitation if we stimulated the center of the receptive field with a very small spot in the fully dark adapted animal. By intensifying this spot latency decreases while the excitation increases. Indeed initially the response consists of excitation without any sign of inhibition, but if the latency reaches about 35 msec the first indications of the presence of inhibition are recognizable. Firstly an

oscillatory pattern of the primary excitation (often with a period of 20 msec) which always indicate the presence of a weak inhibition and finally a clear secondary inhibition arises. Obviously inhibition is present in the center of the receptive field (Rodieck and Stone, 1965) or is elicited by stray light from the intense spot into the surround. So unfortunately the exact relation between latency and original excitation could not be made. This relation, however, continuously decreases.

Secondary activities as a measure of the inhibitory receptive field of tract units

When the receptive field center is stimulated with a spot of 2^{o} only a very weak secondary inhibition and excitation can be seen. Enlarging the spot from 2 to 5^{o} usually causes a clear secondary inhibition and excitation. Increasing the spot diameter still further does not change ON-center responses any more except for the secondary excitation which increases up to stimuli of 10^{o} indicating that the surround extends up to about 10^{o}. However, the OFF-center units show further changes, as mentioned above. The primary excitation decreases while the secondary inhibition also decreases. Only the secondary excitation increases (Fig. 2.2).

The conclusion drawn from these contradictory findings from the OFF-center units was that

- the original excitation increased with increasing spot diameters as suggested by a shortening of the latency to the primary excitation (see preceding paragraph).
- the inhibition produced by the surround also increases as indicated by an increase in the secondary excitation.
- the interaction between the increased excitation and inhibition is changed in such a way that the final result being that the primary excitation and secondary inhibition both decrease.

The most plausible explanation for these findings is that the increased inhibition elicited by increasing spot diameters is shifting forward and partly coincides with the excitation. In ON-center units, on the other hand, the inhibition is appearing when the excitation is already declining and is then capable of producing a clear firing pause. So equal amounts of excitation and inhibition give rise to different responses depending on the temporal interactions.

As pointed out in this paragraph the secondary activities of OFF-center units are increasing up to 20^{o} which

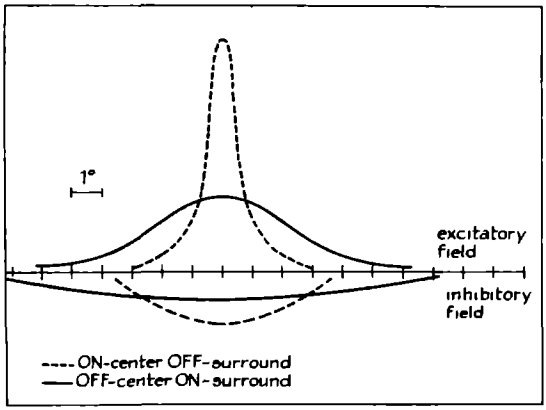

Figure 2.8 *Model of the excitatory and inhibitory receptive fields of optic tract ON-center and OFF-center units. The sizes of the excitatory and inhibitory fields are discussed in the first and second paragraph of the Discussion respectively.*

indicate that the inhibitory receptive fields of OFF-center units are extending between 10 and 20 degrees. In contrast, the inhibitory receptive fields of most ON-center units are in the order of 5 - 10 degrees. Consequently, the sizes of the inhibitory fields corresponds well with the sizes of the excitatory receptive fields.

In Figure 2.8 an attempt is made to draw a model of the receptive fields of both ON- and OFF-center units. This is mainly based on the model given by Rodieck and Stone (1965). Only the sizes and the responsiveness of both types of units are adjusted.

Origin of the differences between ON-center and OFF-center tract units

The majority of the ON-center units (about 70%) show, after a diffuse stimulation, a strong primary excitation followed by a strong or moderate secondary inhibition. The remaining ON-center units and nearly all OFF-center units show a moderate or weak primary excitation and a moderate or weak secondary excitation. There exists a positive correlation between the primary excitation and secondary inhibition (Fig. 2.9). This is also expressed in the general shape of the PSTHs of the ON- and OFF-center units (Figs. 2.5 and 2.6). As mentioned in the preceding paragraph this

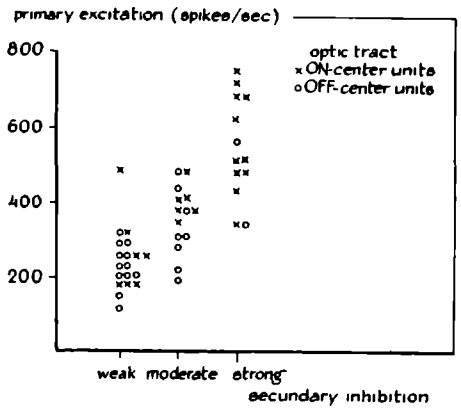

Figure 2.9 *Relation between the primary excitation and secondary inhibition of optic tract units. Note the difference between the majority of ON-center and of OFF-center units.*

is due to a different interaction of the excitatory and inhibitory phenomena in the two types of units. In order to diminish the primary excitation of OFF-center units, the secondary inhibition must have a relatively short latency. It is difficult to determine this latency exactly but it is estimated to be about 35 - 40 msec, in contrast with the latency of the corresponding secondary (surround) excitation which is generally long. Why the latency to the secondary inhibition is so short is unknown, possibly there is a relation with the latency of the primary inhibition of OFF-center units, which is also very short (see also Freund et al., 1970) in contrast with latencies of other primary activities. The correspondence between both findings is that both are inhibitory phenomena of OFF-center units.

Freund et al. (1970) suggest that these phenomena could be mediated through a shorter route than the other characteristics. A second possibility might be that there is a relation with the variable characteristics of the OFF-center receptive fields.

When we say ON- and OFF-center units we mean the majority of the ON- and OFF-center units. As Figure 2.9 shows there are also some ON-center units with a low primary excitation and a low secondary inhibition whereas a few OFF-center units also occur with a strong excitation and inhibition (see also the PSTHs of Figs. 2.5 and 2.6). In this respect the recent paper

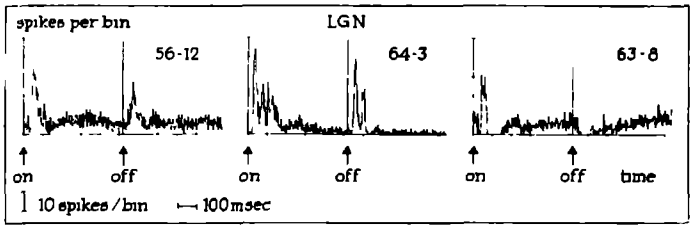

Figure 2.10 *Some LGN-units showing variable characteristics in the PSTHs*

of Fukada (1971) is interesting. He was able to classify particularly the ON-center tract units into a phasic and tonic responding type. This classification was mainly based on the amount of maintained activity of the responses elicited by a spot of 1 degree measured after some seconds. Possibly, their type 1 and 2 correspond to our high-excitatory, strong-inhibitory and low-excitatory weak-inhibitory types respectively. Fukada (1971) found differences in the size of the receptive field center amoung these ON-center types. This indicates that the differences between the ON-center units themselves presumably are based on the same base as the differences between the ON- and OFF-center units as pointed out in this paper.

Characteristics of the intrageniculate inhibition

As mentioned in the results some differences between optic tract and geniculate units are caused by the hyperpolarizations present in the LGN. Two hypotheses exist about the origin of these hyperpolarizations. Burke and Sefton (1966a, b, c) concluded from their experiments that inhibitory connections exist between both synergistic and antagonistic cells, while Singer and Creutzfeldt (1970) propose that these connections exist only between antagonistic cells so only ON- and OFF-center units inhibit each other (reciprocal inhibition).

The existence of inhibitory connections between antagonistic cells seems clear but the connection between synergistic cells was doubted by Singer and Creutzfeldt (1970). In our data, however, some arguments could be found in favour of the hypothesis of Burke and Sefton (1966a, b, c).

Firstly, in quasi-intracellular recordings hyperpolarizing potentials appear during the dominant response period, also when the antagonistic units do not fire. The clearest example shows unit 63-8, an OFF-center unit. Incidently the latency to the

primary excitation of this unit was relatively long, (about 40 msec), and in this case a clear hyperpolarization starting at about 30 msec is recognizable. This inhibition preceding the primary excitation, which could also be seen in the PSTH (Fig. 2.10, unit 63-8), must be caused by firing of other ON-center units because all OFF-center units are strongly inhibited during this period (primary inhibition). Secondly, the secondary inhibition of ON-center units in particular is more increased than that of OFF-center units as compared with the optic tract units. This phenomenon can be related with the fact that the total amount of primary excitation of the ON-center units is much greater than the primary excitation of OFF-center units. It cannot be due to the influence of secondary excitation because they are for both types of units almost identical.

At the moment it is generally accepted that the inhibition is mediated through the interneurons present in the LGN. However, the problem arises whether the input to the interneurons originates from collaterals of the axons of LGN neurons (backward inhibition) as indicated by Burke and Sefton (1966a, b, c), or directly from the optic tract fibres (forward inhibition). Both possibilities are suggested by the histological data of Szenthagothai et al. (1965). In one case (unit 65-2, see Chapter 1) it was possible to measure the exact latencies of the hyperpolarizations when they preceeded the primary excitation of the dominant response period. This latency appeared to be almost equal to the latency of the primary excitation of the input response while the latency of the spikes was considerably larger. We interpret this result as an argument for the existence of forward inhibition.

More information about the interneurons would be available if the responses to visual stimuli of the interneurons were known. In the case that both synergistic and antagonistic inhibition exist, the visual response of an interneuron should show the same latencies both for the light-on and light-off period.

The majority of the LGN units with variable characteristics indeed showed equal latencies for both response periods (Fig. 2.10). Half of these neurons showed short latencies (30 msec), whereas characteristics of these units resembled the added characteristics of ON- and OFF-cells (Fig. 2.10, unit 64-3). So these units might be principal cells receiving their inputs both from an ON- and an OFF-center fibre.

The other half showed relatively long latencies (45 msec, half top value PSTH) and a high and irregularly maintained activity (Fig. 2.10, unit 56-12). Particularly this last group,

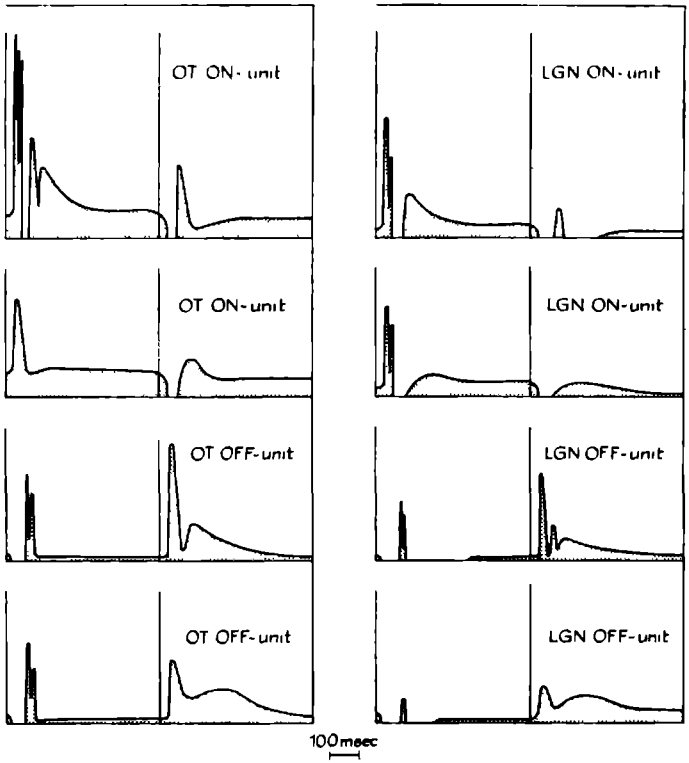

Figure 2.11 *Schematized PSTHs of optic tract and corresponding geniculate responses. Side by side presented histograms suggest a transfer of an optic tract response to an LGN response. Two typical examples both of ON-center and OFF-center units are shown. Special attention is laid on the following three transfer characteristics. Firstly, the lowered responsiveness which could be seen in all geniculate PSTHs. Secondly the extra suppression of the activity in the geniculate non-dominant response period, especially visible in the ON-center units and thirdly the increase in the secondary inhibition in the ON-center geniculate units.*

4% of total units, might fit into the picture of the interneurons, the slowly increasing first excitation suggesting backward inhibition.

In order to test the model of Burke and Sefton (1966b) which was generally confirmed by our data, except that we could not fully exclude the existence of forward inhibition, we did some model experiments. In these experiments an input response of an LGN neuron, obtained from the quasi-intracellular recordings was offered to an electronic neuron simulator. The task of this artificial neuron was to change this input into the output response which was really obtained.

It appeared that a rather good similarity was reached if some parameters such as the amplitude and time constants of the EPSPs were adjusted with only antagonistic inhibition. The similarity was better approximated when synergistic inhibition was also added. It did not matter whether synergistic inhibition was added backward or forward. Consequently in this respect no further insight into the mechanism of intrageniculate inhibition could be obtained (Maes, 1970).

Transfer characteristics of the lateral geniculate neurons

The main difference between the units of the two levels appeared to be a difference in responsiveness to visual stimuli. As pointed out in the preceeding paper this was a result of the fact that most recordings were made under sleep or drowsiness in which the transfer ratio of geniculate neurons is 0.5 - 0.7. The control mechanism seemed to be a regulation of the EPSP amplitude. This control of the output might be an important aspect of the function of the LGN neurons.

Next to a difference in responsiveness some minor differences exist due to the intrageniculate hyperpolarizations, as mentioned in the results, consisting of an extra suppression of the activity in the non-dominant response period and an increased secondary inhibition in the dominant response period shown particularly by ON-center units.

We tried to schematize the input-output relations of LGN units by drawing the responses of optic tract and geniculate response and to present them side by side (Fig. 2.11).

The function of the inhibition in the lateral geniculate nucleus is not very clear. Undoubtedly, this inhibition has a function in preventing further synchronous firing of antagonistic units. In the now generally accepted theory of Jung (1961) and Baumgartner (1961), in which ON-center units

are coding brightness while OFF-center units are coding darkness, it is really important that antagonistic cells do not fire together. In this respect extra suppression of the non-dominant response must be considered. This activity is caused by the center-surround organization which works in favour of a sharpening of simultaneous contrast. However, when a diffuse stimulation is used this organization causes in the non-dominant response period an activity which carries an incorrect signal to the higher visual centers. The increased secondary inhibition in the ON-center units seems then a consequence of the neuronal connections which are necessary for this suppression. The secondary inhibition of the ON-units together with the decreased, but still appreciable, firing of the OFF-units (secondary excitation) could have a psychophysical correlate in the so-called Charpentier interval, a minute dark interval in perception at about the same time after stimulus onset.

The ultimate conclusion about the intrageniculate inhibition must be that its consequences are relatively small and that it is plausible that this inhibition might have other functions which are neglected or could not be measured in this way for example in the mediation of binocular inhibition (Singer, 1970; Sanderson et al., 1971).

Summary

1. Responses of cat's optic tract fibres and geniculate neurons to visual stimuli are analyzed. A description is given of the behaviour of a number of response characteristics on some important stimulus parameters such as the size of the stimulus spot, the background intensity and the state of alertness of the cat.

2. It appears that the first excitation (primary excitation) of the response of a tract fibre to a diffuse stimulation is composed of an excitation of the center and a more or less delayed inhibition of the surround. The latency of the primary excitation seems to be a reliable parameter of the excitation originally elicited by the stimulus.

3. On the base of this parameter for excitation it is found that the excitatory receptive fields of optic tract OFF-center units are, on the average, greater than those of ON-center units. It appears also that the inhibitory receptive fields of OFF-center units are larger than those of ON-center units.

4. The input responses of geniculate neurons, obtained from quasi-intracellular recordings, are almost identical to tract responses. Consequently it is concluded that a geniculate neuron receives its main excitatory input generally from one optic tract fibre. This is also suggested by other data.

5. Transfer characteristics of geniculate neurons are studied by comparing the responses of both levels. The main difference between these responses consists of a decreased responsiveness of the geniculate neurons. As pointed out in the preceeding paper (Chapter 1) this is due to the fact that most responses were recorded when the cat was asleep. During wakefulness the geniculate response approximates to the optic tract response. Some minor differences consisting of an increased suppression of the excitation in some periods are caused by intrageniculate hyperpolarizations.

6. Strong evidence exists that these hyperpolarizations are originating both from ON-center and OFF-center neurons as suggested by Burke and Sefton (1966a, b, c). Whether these hyperpolarizations are caused by forward or backward fibres could not be decided. The function of this intrageniculate inhibition is discussed.

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CHAPTER 3

CAT OPTIC TRACT AND GENICULATE UNIT RESPONSES CORRESPONDING TO HUMAN VISUAL MASKING EFFECTS

Introduction

It has been known for a long time that two rapidly succeeding light flashes modify the perception of each. This phenomenon is called visual or perceptual masking and it is most striking when a strong flash masks a weak flash. The perception of the weak flash, or test flash, is suppressed for a certain time, both when the test flash preceeds the strong flash, or masking flash, and when the test flash follows the masking flash. Backward or retroactive masking is the term used to indicate a diminished perception of a test flash preceding the masking flash while in the case of a diminished vision of a test flash following the masking flash one speaks of forward or proactive masking.

As measured by psychophysical methods the time courses of backward and forward masking are different. The time over which forward masking occurs is longer and its recovery from the masking state proceeds at a slower rate (e.g. Schiller, 1969; Kietzman et al., 1971). Some electrophysiological data has become available from investigations on the mechanism of visual masking since Lindsley (1961) and Fehmi et al. (1969) suggested that these effects also appeared in recordings made in cats and monkeys respectively. A natural question to ask is whether masking effects have a peripheral or central origin (e.g Kietzman et al., 1971).

Evidence was presented by Schiller (1968, 1969) that backward masking was a peripheral effect, because he found masking effects in single units of the lateral geniculate

nucleus. Especially the responses of ON-center units looked similar to observed masking effects. In contrast with this the OFF-center responses were rather problematical in this respect. Nakayama (see Fehmi et al., 1969) in measuring in the optic tract, also observed backward masking and suggested that the mechanism of lateral inhibition is responsible for the effects of backward masking. Forward masking, however, although an essential part of the phenomenon of masking has not been investigated.

The present study was undertaken to see whether the whole masking effect could be traced in electrophysiologically recorded responses, and also to see if the masking mechanism could be localized. Our interest in this problem has been aroused also in connection with the problem of the nature of very short (or iconic) visual memory. Because in this respect it is of interest to know the time over which the retina provides information about flashed light patterns and moreover to have information about the time course of interaction of two successive light patterns yielding interacting traces.

In the present study the responses of single units of both optic tract and lateral geniculate nucleus were investigated under typical masking conditions with cats as experimental animals. It turned out that these recordings showed effects quite comparable with psychophysically observed masking.

Methods

During the experiments cats were paralyzed, no general anaesthesia was used. The EEG showed mostly a pattern of light sleep. Pupils were dilated with atropine and phenylephrine.

Spikes of optic tract fibres and geniculate neurons were recorded by means of electrolyte filled glass micropipettes, stereotaxically inserted into the optic tract and geniculate nucleus. Responses of these units, mostly situated in the central area of the retina, were recorded on magnetic tape and calculated with a digital computer. Presentations of the responses were given in dot-displays and time histograms.

All experiments were carried out under a low level background intensity (0.01 asb). Cats faced a 40 x 40 cm screen, at a distance of 57 cm, on which visual stimuli were given with a Ferranti Cl-63 flash tube. All stimuli, having an intensity of 4 asb, were diffuse i.e. covered the whole screen and were of a green color.

A flash with a duration of 40 msec and an intensity of 4 asb was used as a masking flash whereas the test flash also

had an intensity of 4 asb but its duration was very short (2 msec) giving the impression of a weak flash. The interval between the start of the masking flash and the start of the test flash was called the interstimulus interval (ISI). The ISI was termed negative when the test flash preceeded the masking flash and positive when the test flash followed the masking flash. The test flash could shift, in steps of 10 msec, from an ISI of -70 msec up to an ISI of +220 msec. A general trigger point was chosen to be 80 msec before the masking flash. The repetition frequency was one stimulus pair in 2 seconds. In Figure 3.1 the stimulus time pattern is shown.

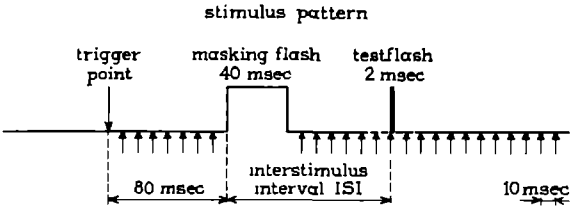

Figure 3.1 Stimulus pattern as used in the experiments. The test flash could occur at the various times indicated by arrows.

Further details of the biological preparation, the recording of spikes and the data analysis are given in two preceeding papers (Chapter 1 and 2).

Results

Electrophysiological results

Responses of 6 units (2 optic tract ON-center, 2 optic tract OFF-center and 2 geniculate ON-center units) are presented in Figure 3.2. In this Figure the dot-displays of the responses to a whole stimulus cycle are shown. PSTHs of the responses of a typical ON- and OFF-center optic tract unit are shown in Figure 3.2.

Let us first consider the responses of an ON- and an OFF-center unit to a single flash. In Figure 3.3 these responses can be seen in the case when the ISI = 0 msec. The response of the ON-center unit, which has a latency of about 30 msec, consists of a primary excitation (30 - 80 msec) followed by an inhibition (80 - 130 msec) which is in turn followed by a secondary excitation. The response of an OFF-center unit is

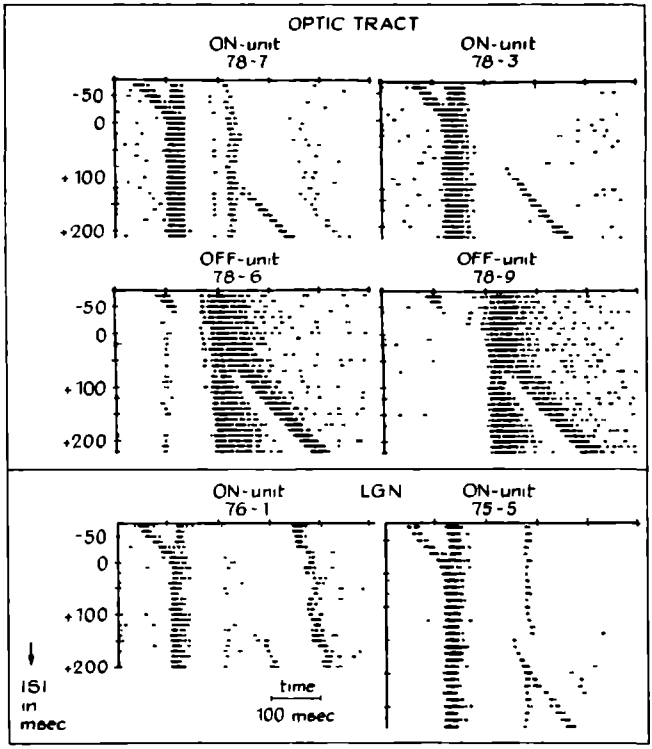

Figure 3.2 *Dot-displays of the responses of 6 units. Spikes are presented as dots. ISI is indicated on the ordinate. Traces always start after a trigger at 80 msec before the masking flash (Figure 3.1). The test flash begins at -70 msec and is shifted by 10 msec every following trace. Only the first 500 msec of the response after the trigger is shown.*

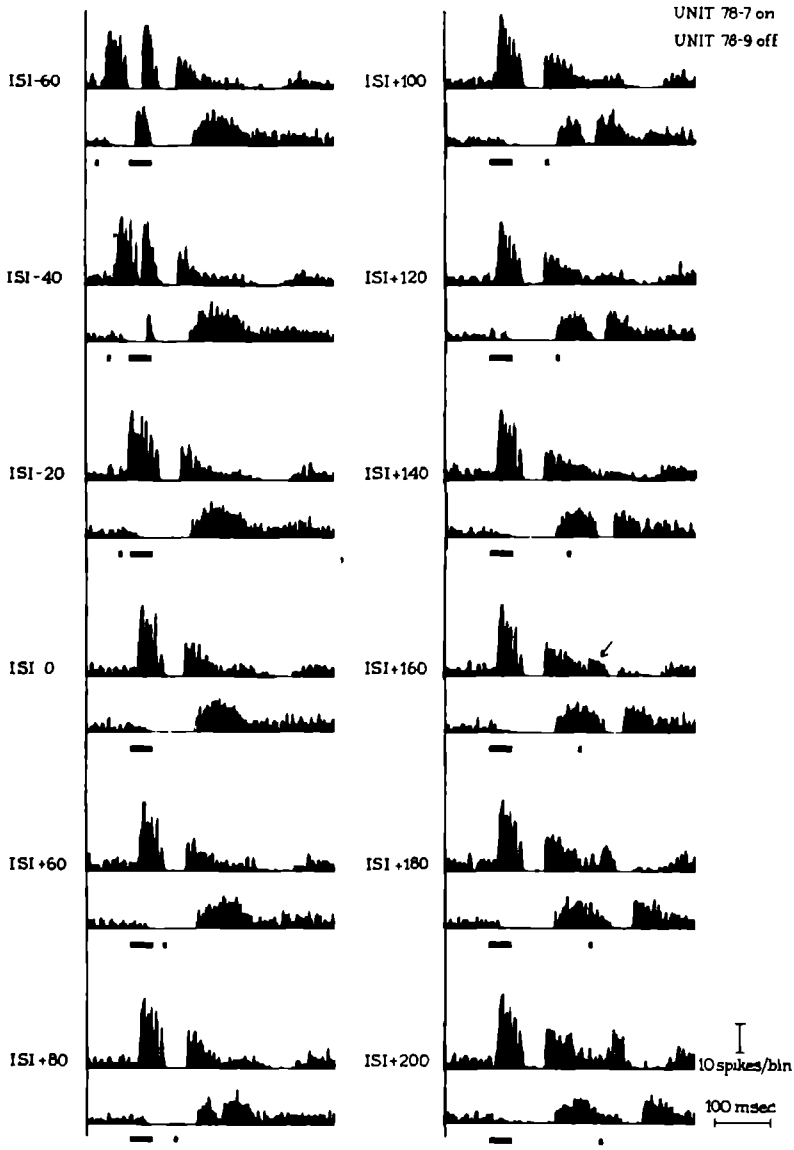

Figure 3.3 PSTHs of the responses of an ON-center unit (78-7), upper row of each pair, and an OFF-center unit (78-9), lower row of each pair. Masking flash is indicated as a black line whereas the test flash is indicated by a black dot. PSTHs were composed by averaging 10 sweeps. Note the arising ON-center activity of the test flash at an ISI of +160 msec (arrow).

basically composed of a prolonged inhibition, beginning at about 30 msec and lasting up to about 100 msec. This inhibition is followed by an excitation.

The response to a shorter single flash, such as the test flash, is generally the same, except that the activities are smaller. Latency differences between the excitations of the masking flash and the test flash are generally small, of the order of some milliseconds.

These responses fully agree with the responses to single short flashes as described by Grüsser and Rabelo (1958), although these were obtained while the cat was adapted to a higher background intensity than in our experiments.

Backward masking

The experiment started with the test flash preceeding the masking flash by 70 msec. Initially the response of an ON-center unit to these paired flashes consists of two primary excitations separated by an inhibitory period. When the ISIs are getting shorter the two primary excitations are shifted together. At an ISI of about -30 msec the end of the first primary excitation, elicited through the test flash, reaches the beginning of the second primary excitation caused by the masking flash. At first the combined excitation is somewhat longer but the responses at ISIs of about -10 msec are identical to the response of the masking flash alone (Fig. 3.2).

Similarly to the ON-center units, the response of the OFF-center units initially (ISI = -70 msec) consists of two excitations. The first OFF-excitation, between the two primary excitations of the ON-center units, decreases when these ON-center unit excitations are shifting together. As soon as the ON-center primary excitations are touching each other (ISI = -30 msec), the first OFF-center excitation which originated from the test flash is fully abolished, only the excitation of the OFF-cell elicited by the masking flash can be seen.

Consequently, we concluded that electrophysiological backward masking in the optic tract occurs when the test flash preceeds the masking flash by about 30 milliseconds.

Forward masking

No change in the response of the ON-center units could be detected up to ISIs of about +80 to +90 msec. Obviously the inhibition elicited by the masking flash suppresses the excitation of the test flash. Hereafter a small activity of

the test flash could often be seen but this activity was drowned into the secondary activity of the masking flash. From ISIs of about +160 msec the primary excitation of the test flash is clearly separated from the secondary activity of the masking flash (see unit 78-8, Figs. 3.2 and 3.3 arrow).

In a minority of units, amounted to about 25% of the recorded optic tract units, the secondary excitation was absent (unit 78-3, Fig. 3.2). In these units the primary excitation of the test flash was visible when the primary excitation of the test flash dominated the inhibition of the masking flash.

The investigated lateral geniculate units behaved like the majority of optic tract units (units 76-1 and 75-5, Fig. 3.2).

The OFF-center responses were also unchanged up to ISIs of about +80 msec. Subsequently the OFF-excitation of the masking flash was incised by the OFF-inhibition of the test flash. This process further led to the existence of two OFF-excitations separated through an inhibition (units 78-9 and 78-6, Figs. 3.2 and 3.3). During this inhibition of the OFF-center unit the primary excitation of the ON-center unit becomes visible at ISIs of about +160 msec (Fig. 3.3).

The conclusion drawn from these experiments is that electrophysiological forward masking in the optic tract responses of ON-center units occurs up to ISIs of about 160 msec. The responses of the OFF-center units will be discussed later.

Psychophysical methods and results

Three experienced subjects participated in the psychophysical experiments. They viewed the same visual stimuli as employed in the electrophysiological experiments. The stimulus consisted of either a masking flash alone or of a masking flash paired with a test flash. The masking flashes and the paired flashes with different ISI were given in a random sequence. The subjects were asked to indicate whether they observed a single masking flash or a pair of flashes. They did so by indicating their level of confidence of observing the test flash. So their answer could be one of the following four alternatives: 1) test flash clearly seen 2) test flash probably present 3) test flash possibly present 4) no test flash. Every kind of stimulus was given 80 - 100 times during a complete series. So a complete series consists of about 600 stimuli divided over 6 different ISIs and one 'only masking

flash' condition. As the experimental result of a series one obtains: 1) the probability of the test flash being seen clearly 2) the probability of the test flash being perceived with at least medium confidence 3) the probability of the test flash being perceived with the low confidence cases also included. In this way three psychometric curves can be constructed (Fig. 3.4), which show the probability of perception of the test flash as a function of the ISI at different levels of confidence. Note that the vertical scale is a normal probability scale. This is done in order to obtain a graph for which the vertical scale is linear to the perceived magnitude of the neural signal representative for the test flash. Moreover

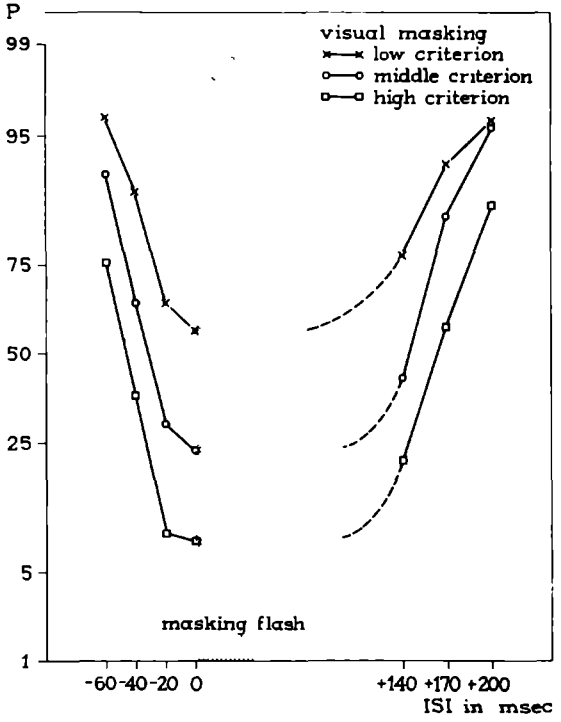

Figure 3.4 Three psychometric curves showing the probability of detecting the test flash according to three different criterion values meeting the different levels of confidence of detection.

the three psychometric curves offer the opportunity to estimate the fluctuation decisive for the report of the subjects

(Eijkman, 1970). Figure 3.4 shows the curves averaged for three subjects. It appears that backward masking starts at 60 msec before the masking flash and increases up to about 20 msec before the masking flash. Secondly forward masking shows itself fully up to about 110 msec after the masking flash and gradually diminishes up to about 200 msec after the masking flash. Finally, besides the detectability of the test flash, one obtains a measure of the fluctuation of this detectability of the test flash during the time course of the masking effect. It follows from the vertical distances between the three psychometric curves that the fluctuation in detectability of the test flash is about the same for backward and for forward masking.

Comparing these results with the electrophysiological recordings one can certainly observe a great similarity in the time course of the masking effect apparent in both kinds of measurements.

At this point it may be useful to make two critical remarks about this comparison. Firstly, we compare peripheral neural signals of the cat with human perception of a more central origin and secondly, we compare mean single unit activity in the cat with a mean of simultaneous activity of many units in the human visual system. The problems connected with this comparison will be discussed later. At this moment we may question whether we find the same kind of fluctuations in the observability of the test flash in the electrophysiological recordings as compared with the psychophysical results. Instead of observing many units many times we may judge the activity of a single unit many times. To this end the same three subjects inspected several recordings of a single geniculate ON-center unit (unit 75-5, Fig. 3.2). After they felt themselve to have enough experience to detect the presence of the test flash in these recordings, they were asked to inspect several randomly mixed single responses and state their confidence in respect to the detection of the test flash in quite the same way as they had done in the psychophysical experiments. Again three probability curves can be constructed but now for the probability of detecting the test flash by visual examination of the spike recordings in single responses. The result is shown in Figure 3.5. Also in this case the masking effect is clearly observable. The course of the masking effect as a function of the ISI is not very much different from the one shown in Figure 3.4. Again the fluctuation in observability of the test flash appears to be the same for backward and for forward masking.

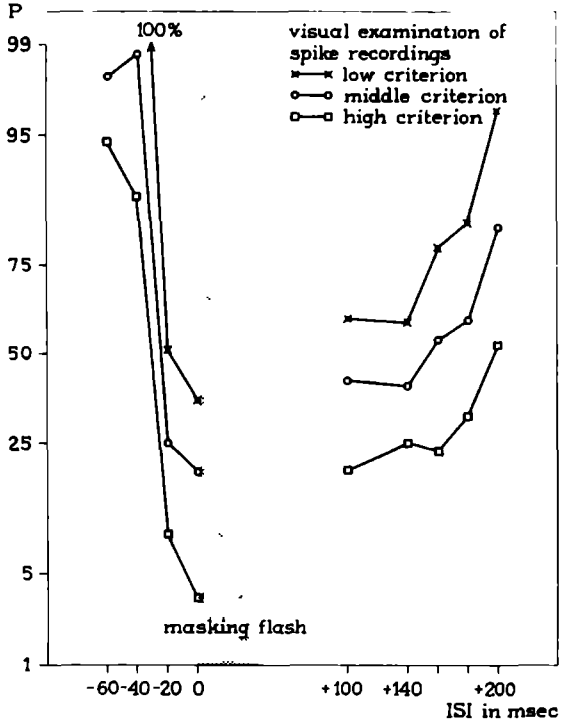

Figure 3.5 *Three curves representing the probability of detection of test flashes by means of visual inspection of single traces of spike recordings taken from a geniculate ON-center neuron (unit 75-5) of the cat.*

We may summarize this result by stating that detection of a masked test flash in the human visual system shows results which are very similar to the single unit ON-response in the peripheral visual system of the cat.

Discussion

As mentioned above the results obtained from ON-center units correspond very well to both backward and forward masking. Also OFF-center units fit into this picture. There is one difference, however, in that forward masking for these units ends at shorter ISIs (at about +80 to +90 msec).

Both ON- and OFF-units were analyzed together in consideration of the theory of Jung (1961) and Baumgartner

(1961) regarding the fact that both types of units are working together in achieving perception (ON-units coding light-on or brightness, OFF-units coding light-off or darkness). In Fig. 3.3 the PSTHs of a representative ON- and OFF-center unit are presented in pairs which allows us a good comparison. It turned out that in the range of ISIs of -20 to +160 msec, in which psychophysically one flash is perceived, the firing of the ON-center units is followed by the firing of the OFF-center units. For ISIs outside the range of -40 and +160 msec, in which psychophysically two flashes are perceived, it appeared that the firing sequence is: ON-units, OFF-units, ON-units and again OFF-units. This succession of activities seems to provide the necessary condition for observing two separate flashes. This means that also when the ON-unit fires with two subsequent bursts (e.g. ISI = 0 msec, primary and secondary excitation respectively) which are not separated by an excitation of the OFF-unit only one flash will be perceived. This is in full agreement with the theory described above.

Accordingly it was concluded that the time course of all masking phenomena is due to intraretinal mechanisms only and that, in this respect, no additional central properties are required. These findings confirmed the measurements of Schiller (1968, 1969) who found that responses of geniculate ON-center units could be correlated with backward masking and stipulated that forward masking, for which the times are considerably longer, could also be found at a peripheral level. The somewhat remarkable behaviour of the OFF-center geniculate neurons in the work of Schiller (1968) might possibly be due to the use of the barbiturate anaesthesia.

From the comparison between tract responses and perception it appeared that the responses of single units often have a somewhat sharper temporal resolution compared with the perceptive data. The temporal characteristics of different units, however, are not completely identical. So adding up many of these units could explain why the graph of the psychophysical results is smoother than the graph obtained from the electrophysiological results (Figs. 3.4 and 3.5).

This brings us to the problem of comparing electrophysiological results of single units of the cat with the many units cooperating for a visual perception in man. No data are available concerning the time course of single units activity in the optic tract of man. Therefore we might compare responses of the cat with those in the monkey which is closely related to man. As the responses after a flash in cat and monkey do not show much difference with respect to the time course of the activity (Hubel and Wiesel, 1960) we feel justified in assuming that

single units in the human visual system behave similarly to single units in the cat. On the other hand cats as suggested by Lindsley (1961) and monkeys as suggested by Fehmi et al. (1969) show comparable masking effects as judged from their behaviour. Granted the assumption that single units in the cat show an activity with a time course comparable to those in man we are left with the extrapolation from some single units to a many units system. Fortunately the differences between the single units are relatively small, so the total effect in the optic nerve may be described approximately as the addition of quite similar activities of two kinds: ON-activity and OFF-activity. This allows us to compare single unit activity with an integrated activity of many units as revealed by our psychophysical experiments. However, whereas the psychophysical experiments produce numerical values for the detectability of the test flash, the electrophysiological data will not readily yield comparable figures, because we do not know how the information supplied by the optic tract will be processed centrally. In order to obtain at least a partial solution to this problem we have used human observers as 'pattern recognizers' for the detection of the existence of a test flash in the electrophysiological recordings of single traces. Now again we obtain a measure of the detectability of the test flash assuming that human 'pattern recognizers' do similar things with cat spikes as the cat itself does.

As shown in Figures 3.4 and 3.5 we have obtained similar detectabilities of the test flash. Minor differences are probably to be expected because Fig. 3.5 is the result of judging many traces of a single unit, whereas Fig. 3.4 is the result of judging repeatedly the simultaneous activity of many units. Another point of interest is the fact that fluctuations in the report of the test flash apparent both in forward and in backward masking are about the same. This is true for single unit inspection as well as for many units inspection.

Mechanisms responsible for visual masking

Mainly two effects are responsible for backward visual masking. Firstly the primary excitation of ON-center units elicited by the test flash lasts for a minimum of about 40 to 50 msec. Levick and Zacks (1970) pointed out that this minimal duration was independent of the duration of the response to the test flash. This relatively long duration of the test flash means that at an ISI of about 30 to 40 msec the excitation of the test flash reaches the excitation of the masking flash. At

the same time the response of the OFF-center unit is suppressed when the two ON-center bursts reach each other. Obviously an inhibitory path between the ON-center and OFF-center units exists. In Fig. 3.3 this suppression of the OFF-excitation becomes clearly visible at ISIs of -60 up to -20 msec.

Forward masking is caused by the suppression of the ON-excitation of the test flash through the inhibition existing at the ON-units caused by the masking flash at ISIs of +40 up to +80 msec. On the other hand the interaction of the increasing activity of the primary excitation of the test flash with the secondary excitation of the masking flash is responsible for the further course of forward masking up to ISIs of 140 to 160 msec. A short investigation was carried out on the origin of both the inhibition and the secondary excitation of the ON-center units. The results of this investigation, using different stimulus durations, suggested that both phenomena are effects of lateral inhibition, the ON-inhibition being the effect of the surround after 'light-on' while the secondary excitation seems to be the effect of the surround after 'light-off' (see also Chapter 2).

It should be noticed that these effects also appear, although with other temporal characteristics, when two flashes of equal intensity and duration are used. Indeed, this was already shown by Grüsser and Kapp (1958) and Levick and Zacks (1970).

Summary

1. Stimuli leading to backward and forward visual masking in man were presented to the cat. Responses of single units in the optic tract and the lateral geniculate nucleus were measured.

2. The results of these measurements have been compared with human psychophysical data obtained under the same stimulus conditions. The possibility of comparison the two kinds of data is discussed.

3. From this comparison it is concluded that the time course of both backward and forward masking is fully determined by mechanisms localized in the retina. The response duration and the antagonistic behaviour of ON- and OFF-center units are responsible for backward masking whereas the effects of the lateral inhibition may be responsible for forward masking.

4. Some suggestions are done in order to explain how the perception is mediated by the cooperation of the signals of ON- and OFF-units. Firstly, firing of the ON-units followed by firing of the OFF-units is the condition necessary for the perception of one brief flash. Secondly, two rapidly succeeding ON-excitations which are not separated by an OFF-excitation do not lead to the perception of separate flashes.

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SAMENVATTING

Het belangrijkste doel van dit onderzoek was om gegevens te verkrijgen over de rol van het corpus geniculatum laterale (CGL) in de overdracht van de visuele informatie van de retina naar de visuele cortex. Het meten van de relatie tussen input en output van 'single units' is een bekende manier om deze informatie te verkrijgen. De hoofdstukken 1 en 2 geven ieder een methode om dit te doen.

In hoofdstuk 1 worden zogenaamde 'quasi-intracellulaire' metingen aan neuronen van het CGL verricht. Met deze methode, waarbij de microelectrode vrijwel tegen het membraan gelegen is, zijn naast de actiepotentialen ook de excitatieve en inhibitieve postsynaptische potentialen (EPSPs en ISPSs) te meten. Het bleek dat de EPSPs zich manifesteerden in twee vormen de onderdrempelige EPSPs en de bovendrempelige EPSPs. De laatste zijn niet meer als zodanig herkenbaar maar zijn veranderd in actiepotentialen. De input is nu het totale aantal EPSPs terwijl de output eenvoudig het aantal actiepotentialen is. De relatie tussen input en output werd uitgedrukt in de overdrachtsverhouding ('transfer ratio') gedefinieerd als het quotient tussen de gemiddelde frequentie van de output en de gemiddelde frequentie van de input bepaald uit de responsies op lichtstimuli. Deze overdrachtsverhouding bleek sterk afhankelijk te zijn van het bewustzijnsniveau van het proefdier. De proefdieren, die niet geanaesthetiseerd maar geparalyseerd waren, verkeerden meestal in een toestand van slaap die afgewisseld werd met 'drowsiness', een toestand tussen slapen en waken. Meestal kan echter een 'arousal' reactie opgewekt worden door proprioceptieve stimuli (b.v. door het proefdier aan te raken). Na een dergelijke stimulus verandert het EEG van een slaappatroon in een alert patroon. De grootte van de responsie op een lichtflits van een neuron in het CGL neemt dan aanzienlijk toe. De input blijft echter constant. De overdrachtsverhouding die ca 0,4 - 0,5 bedraagt gedurende slaap stijgt tot 0.9 - 1,0 gedurende waakzaamheid met tussenliggende waarden voor 'drowsiness'.

Dit betekent dat gedurende waakzaamheid vrijwel alle visuele informatie doorgelaten wordt naar de hogere visuele centra, terwijl gedurende slaap een groot gedeelte geblokkeerd wordt op dit niveau. Deze regulatie, vermoedelijk gestuurd door de reticulaire formatie, is waarschijnlijk een belangrijke functie van het CGL.

In dit hoofdstuk wordt ook ingegaan op het mechanisme van deze regulatie. Gevonden werd dat een regeling van de amplitude van de EPSPs optreedt. Gedurende waakzaamheid is de amplitudo van nagenoeg alle EPSPs voldoende groot om de drempelwaarde te bereiken, terwijl gedurende slaap de EPSPs kleiner zijn dan de drempelwaarde.

De methode om via de quasi-intracellulaire metingen de input-output relatie te bestuderen heeft echter het nadeel dat, vanwege technische moeilijkheden, slechts weinig neuronen gemeten kunnen worden. In hoofdstuk 2 wordt op een andere manier de input-output relatie van de corpus geniculatum neuronen onderzocht. De input van de CGL neuronen kan namelijk ook gemeten worden aan de vezels van de tractus opticus. Deze responsies kunnen dan, op een statistische manier, vergeleken worden met de responsies van de geniculatum neuronen. Deze vergelijking was des te aantrekkelijker omdat uit hoofdstuk 1 sterke aanwijzingen verkregen werden dat een CGL neuron zijn input ontvangt van slechts één tractus opticus vezel wat de interpretatie aanzienlijk vergemakkelijkt.

De responsies van zowel de CGL neuronen als de tractus opticus vezels werden eerst afzonderlijk bestudeerd. Om meer inzicht te verkrijgen in deze responsies werd het gedrag van een aantal karakteristieken in deze responsies op enige belangrijke stimulusparameters bestudeerd. Zo werd de invloed op de responsie van de grootte van het stimulusoppervlak, van de achtergrondintensiteit en van het bewustzijnsniveau van het proefdier nagegaan. De karakteristieken van de responsie afkomstig van de twee delen van het receptieve veld, het centrum ('center') en de periferie ('surround') zijn te herkennen op basis van de latentietijden. De primaire activiteiten afkomstig van het centrum hebben een korte latentietijd, terwijl de secondaire activiteiten, afkomstig van de periferie, lange latentietijden hebben. Een belangrijke conclusie was dat op retinaal niveau de latentietijd van de primaire excitatie een betrouwbare parameter is voor de oorspronkelijke excitatie veroorzaakt door de stimulus, terwijl de primaire excitatie zelf opgebouwd is uit excitatie afkomstig van het centrum, vermindert met meer of minder vertraagde

inhibitie, afkomstig van de periferie. Met gebruikmaking van deze parameter voor de excitatie werd gevonden dat de OFF-center ON-surround units grotere excitatieve velden hebben dan de ON-center OFF-surround units. Ook de inhibitieve receptieve velden van OFF-cellen bleken aanmerkelijk groter te zijn dan die van ON-cellen.

Uit een vergelijking van de tractus opticus responsies met de CGL responsies bleken een drietal verschillen te bestaan die alle van inhibitoire aard waren. Het eerste was het reeds in hoofdstuk 1 gememoreerde verschil in responsiviteit op de stimulus, te wijten aan het feit dat de meeste afleidingen gemaakt zijn als het proefdier verkeerde in een toestand van slaap. De andere twee verschillen zijn kleiner en bestaan uit een extra onderdrukking van de activiteit in bepaalde perioden van de responsie, zoals in de zgn. non-dominante periode en gedurende de fase van de secundaire inhibitie van de dominante periode. Beide verschillen worden veroorzaakt door een inhibitiemechanisme in het CGL. Het onderzoek naar het werkingsmechanisme hiervan is het laatste punt van hoofdstuk 2. In grote lijnen werd het inhibitiemodel geponeerd door Burke en Sefton bevestigd.

Over de functie van dit inhibitiemechanisme is gediscussieerd. Mogelijk is dat het onderdrukken van de activiteit in de non-dominante periode, als zijnde een incorrect signaal voor de hogere visuele centra, een functionele betekenis heeft.

In hoofdstuk 3 werd de visuele maskering, zoals die voorkomt bij proefpersonen als twee lichtflitsen elkaar snel opvolgen, onderzocht. De responsies van het perifere visuele systeem (tractus opticus en CGL van de kat) verkregen onder gelijke stimuluscondities, werden daartoe geanalyseerd. Beide typen maskering, zowel de achterwaartse als de voorwaartse maskering kunnen gezien worden in deze electrofysiologische responsies. Uit de analyse van deze responsies blijkt dat het tijdsverloop van deze maskering geheel bepaald wordt op retinaal niveau. Voor achterwaartse maskering zijn vooral de duur van de responsie en de inhibitoire interactie tussen ON- en OFF-center units verantwoordelijk, terwijl de effecten van de laterale inhibitie de voorwaartse maskering grotendeels kunnen verklaren. Tevens zijn enige belangrijke suggesties gedaan over de verwerking van de gegevens van ON- en OFF-center units door de hogere visuele centra die uiteindelijk de perceptie bepalen.

Nader wordt ingegaan op de vraag in hoeverre de gegevens over de perceptie van proefpersonen vergeleken kunnen worden met de electrofysiologische gegevens verkregen bij de kat.

S T E L L I N G E N

- 1 -

Het periferie effect, beschreven door McIlwain, heeft geen perceptieve betekenis.
McIlwain, J.T., J. Neurophysiol. 27, 1154-1173 1964.
Moors, J. Intern rapport, Lab. v. Med. Fysica 1971.

- 2 -

Een snel inzicht in de invloed van een bepaalde stimulusparameter op de responsie is te verkrijgen door deze parameter gedurende stimulatie geleidelijk te veranderen en de responsies weer te geven in een "dot-display".
Dit proefschrift, figuren 2.3 en 3.2.

- 3 -

Het optreden van hyperpolarisaties in de responsies van neuronen in het corpus geniculatum laterale voorafgaande aan de primaire excitatie wijst duidelijk op synergistische inhibitoire interacties in deze kern.
Dit proefschrift, pag. 53 en 54.

- 4 -

Electrofysiologische modelexperimenten zijn vooral zinvol indien zij gekoppeld zijn aan lopend electrofysiologisch onderzoek. Zij zijn met name geschikt om nieuwe vragen te creëren voor dit onderzoek.

- 5 -

De veronderstelling dat intraveneus ingespoten flaxédil een directe invloed op de hersenen heeft is onjuist.
Halpern, L.M., Black R.G., Science 155, 1685-1687 1967.
Crawford, J.M., Curtis, D.R., J. Physiol. 186, 121-138 1966.

- 6 -

Het lijkt mogelijk om door middel van een goede planning en een reële wil tot samenwerking een meer intensief gebruik te maken van de kostbare apparatuur die nodig is voor het doen van electrofysiologisch onderzoek.

- 7 -

Om interpreteerbare "single unit" gegevens van sensorische systemen te verkrijgen is het wenselijk om met proefdieren te experimenteren die bij bewustzijn zijn. Uit technische overwegingen en vooral uit ethisch oogpunt is het wenselijk om met gedepresseerde proefdieren te werken. Het vinden van een geschikt compromis is belangrijk voor verder neurofysiologisch onderzoek.

- 8 -

Het verdient aanbeveling om onderzoek te stimuleren naar de mogelijkheden om gededifferentieerde cellen van een weefselkweek tot differentiatie te brengen.

- 9 -

Het visuele systeem van de kat lijkt geschikt om televisiebeelden waar te nemen. De geringe belangstelling van katten voor dit medium kan derhalve niet verklaard worden uit het feit dat hun waarnemingsvermogen onvoldoende is.

A.M.L. Coenen
13 december 1971